SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Filspari 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Filspari 400 mg film-coated tablets

Each tablet contains 400 mg of sparsentan.

Excipient with known effect

Each tablet contains 84 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Filspari 400 mg film-coated tablets

White to off-white, oval□shaped, film-coated tablet, debossed with “021” on one side and plain on the other side. The dimensions of the tablets are approximately 18 mm × 8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥ 1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g, see section 5.1).

4.2 Posology and method of administration

Posology

Sparsentan treatment should be initiated at a dose of 200 mg once daily for 14 days and then increased to a maintenance dose of 400 mg once daily, dependent upon tolerability.

For titration from the initial dose of 200 mg once daily to the maintenance dose of 400 mg once daily, 200 mg and 400 mg film-coated tablets are available to achieve the maintenance dose.

If patients experience tolerability issues (systolic blood pressure [SBP] ≤ 100 mmHg, diastolic blood pressure ≤ 60 mmHg, worsening edema, or hyperkalaemia), adjustment of concomitant medicinal products, followed by temporary down–titration or discontinuation of sparsentan is recommended (see sections 4.4 and 5.1).

When resuming treatment with sparsentan after interruption, repeating the initial dosing schedule may be considered. Interruption of treatment preceded, or not by dose reduction of sparsentan, may be considered based on persisting hypotension or changes in liver function (see section 4.4).

Missed dose

If a dose is missed, the dose should be skipped and the next dose is to be taken at the regularly scheduled time. Double or extra doses should not be taken.

Special populations

Elderly

No dose adjustment is recommended in elderly patients (see section 5.2). In elderly patients sparsentan treatment should be initiated at a dose of 200 mg once daily for 14 days. The increase to a maintenance dose of 400 mg once daily should be performed with caution, based on tolerability (see section 4.4).

Hepatic impairment

Based on pharmacokinetics data, no dose adjustment of sparsentan is required in patients with mild or moderate hepatic impairment (Child-Pugh A or Child-Pugh B classification; see section 5.2).

There is limited clinical experience with moderate hepatic impairment. Therefore, sparsentan should be used with caution in these patients (see section 4.4).

Sparsentan has not been studied in patients with severe hepatic impairment (Child-Pugh C classification) and is therefore not recommended for use in these patients.

There is limited clinical experience with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) values more than two times the upper limit of the normal range (ULN). Therefore, sparsentan should not be initiated in patients with AST/ALT > 2 × ULN (see section 4.4).

Renal impairment

No dose adjustment is required in patients with mild (chronic kidney disease [CKD] stage 2; estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2) or moderate (CKD stages 3a and 3b; eGFR 30 to 59 mL/min/1.73 m^2) kidney disease. Based on pharmacokinetic data, no dose adjustment can be recommended for patients with severe kidney disease (CKD stage 4; eGFR < 30 mL/min/1.73 m^2) (see section 5.2). As there is limited clinical experience in patients with severe kidney disease, sparsentan is not recommended in these patients (see section 4.4).

Sparsentan has not been studied in patients who have received a kidney transplant, therefore sparsentan should be used with caution is these patients.

Sparsentan has not been studied in patients undergoing dialysis. Initiation of sparsentan is not recommended in these patients.

Paediatric population

The safety and efficacy of Filspari in children below the age of 18 years with IgAN have not yet been established. No data are available.

Method of administration

Oral use.

It is recommended to swallow the tablets whole with water to avoid bitter taste. Sparsentan can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Pregnancy (see sections 4.4 and 4.6)
- Coadministration of angiotensin receptor blockers (ARBs), endothelin receptor antagonists (ERAs), or renin inhibitors (see sections 4.4 and 4.5)

4.4 Special warnings and precautions for use

Women of childbearing potential

Sparsentan treatment must only be initiated in women of childbearing potential when the absence of pregnancy has been verified and effective contraception is practised (see sections 4.3 and 4.6).

Hypotension

Hypotension has been associated with the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, including sparsentan. Hypotension may occur during treatment with sparsentan and is reported more frequently in elderly patients (see section 4.8).

In patients at risk for hypotension, eliminating or adjusting other antihypertensive medicinal products and maintaining appropriate volume status should be considered. If hypotension develops despite elimination or reduction of other antihypertensive medicinal products, dose reduction or dose interruption of sparsentan should be considered. A transient hypotensive response is not a contraindication to further dosing of sparsentan; treatment can be resumed once blood pressure has stabilised.

If hypotension persists despite elimination or reduction of antihypertensive medicinal products, sparsentan dosing should be reduced to the initial starting dose until blood pressure stabilises. Dose interruption of treatment with sparsentan should be considered if symptoms of hypotension persist after 2 weeks of dose reduction. Sparsentan should be used with caution in patients with systolic blood pressure values ≤ 100 mmHg (see section 4.2). Sparsentan should not be uptitrated in patients with systolic blood pressure values ≤ 100 mmHg (see section 4.2).

Impaired kidney function

A transient increase in serum creatinine has been associated with RAAS inhibitors, including sparsentan. A transient increase in serum creatinine may occur, especially

when initiating treatment with sparsentan (see section 4.8). Periodic monitoring of serum creatinine and serum potassium levels should be performed in patients at risk. Sparsentan should be used with caution in patients with bilateral renal artery stenosis.

Due to the limited clinical experience in patients with an eGFR < 30 mL/min/1.73 m^2, sparsentan is not recommended in these patients (see section 4.2).

Fluid retention

Fluid retention has been associated with medicinal products that antagonise the endothelin type A receptor (ETAR), including sparsentan. Fluid retention may occur during the treatment with sparsentan (see section 4.8). If fluid retention develops during treatment with sparsentan, treatment with diuretics is recommended, or the dose of existing diuretics should be increased before modifying the dose of sparsentan. Treatment with diuretics can be considered in patients with evidence of fluid retention before the start of treatment with sparsentan.

Sparsentan has not been studied in patients with heart failure. Therefore, sparsentan should be used with caution in patients with heart failure.

Liver function

Elevations in ALT or AST of at least 3 × ULN have been observed with sparsentan (see section 4.8). No concurrent elevations in bilirubin > 2 × ULN or cases of liver failure have been observed in sparsentan-treated patients. Therefore, to reduce the risk of potential serious hepatotoxicity, serum aminotransferase levels and total bilirubin should be monitored prior to initiation of treatment and then continue monitoring every three months.

Patients should be monitored for signs of hepatic injury. If patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g, jaundice), sparsentan therapy should be discontinued.

Consider re-initiation of sparsentan only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients without clinical symptoms of hepatotoxicity. Avoid initiation of sparsentan in patients with elevated aminotransferase (> 2 × ULN) prior to drug initiation (see section 4.2).

There is limited clinical experience with moderate hepatic impairment. Therefore, sparsentan should be used with caution in these patients (see section 4.2).

Dual blockade of the Renin Angiotensin Aldosterone System (RAAS)

There is evidence that the concomitant use of Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers (partly a mechanism of sparsentan) or renin inhibitors is therefore not recommended (see sections 4.5 and 5.1). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Hyperkalaemia

Treatment should not be initiated in patients with serum potassium level > 5.5 mmol/l. As with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with sparsentan, especially in the presence of renal impairment and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended. If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is > 5.5 mmol/l discontinuation should be considered.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with ARBs, ERAs and renin inhibitors

Concomitant use of sparsentan with ERAs such as bosentan, ambrisentan, macitentan, sitaxentan, ARBs such as irbesartan, losartan, valsartan, candesartan, telmisartan, or renin inhibitors such as aliskiren is contraindicated (see section 4.3).

Concomitant use with ACE and mineralcorticoid receptor inhibitors

Coadministration of sparsentan with mineralocorticoid (aldosterone) receptor inhibitors such as spironolactone and finerenone is expected to be associated with increased risk of hyperkalaemia.

There are no data on the combination of sparsentan with ACE inhibitors such as enalapril or lisinopril. Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see section 5.1).

The use of sparsentan in combination with ACE inhibitors such as enalapril or lisinopril should be done with caution, and blood pressure, potassium, and kidney function should be monitored (see section 4.4).

Concomitant use with potassium supplements and potassium-sparing diuretics

As hyperkalaemia may occur in patients treated with medicinal products that antagonise the angiotensin II receptor type 1 (AT_1R) (see section 4.8), concomitant use of potassium supplements, potassium-sparing diuretics such as spironolactone, eplerenone, triamterene or amiloride, or salt substitutes containing potassium may increase the risk of hyperkalaemia and is not recommended.

Effect of other medicinal products on sparsentan

Sparsentan is primarily metabolised by cytochrome P450 (CYP)3A.

Strong and moderate CYP3A inhibitors

Co-administration of sparsentan with itraconazole (strong CYP3A inhibitor) increased sparsentan maximum plasma concentration (C_{max}) by 1.3-fold and area under curve from zero extrapolated to infinity ($AUC_{0\text{-}inf}$) by 2.7-fold. Co-administration with a strong CYP3A inhibitor such as boceprevir, telaprevir, clarithromycin, indinavir, lopinavir/ritonavir, itraconazole, nefazodone, ritonavir, grapefruit and grapefruit juice is not recommended. If use of a strong CYP3A inhibitor cannot be avoided, consider interrupting treatment with sparsentan. Treatment with sparsentan can be resumed following discontinuation of the strong CYP3A inhibitor.

Co-administration of sparsentan with ciclosporin (moderate inhibitor of CYP3A) increased sparsentan C_{max} by 1.4-fold and $AUC_{0\text{-}inf}$ by 1.7-fold. Co-administration with a moderate CYP3A inhibitor such as conivaptan, fluconazole and nelfinavir inhibitor should be done with caution. When using a moderate CYP3A inhibitor, patients should be monitored for hypotension, hyperkalaemia, edema, and/or kidney function.

CYP3A inducers

Sparsentan is a CYP3A substrate. Co-administration of sparsentan with a moderate CYP3A inducer (efavirenz) resulted in a decrease in $AUC_{0\text{-}inf}$ and C_{max} of sparsentan by 62% and 38%, respectively. Due to the potential for decreased therapeutic efficacy of sparsentan, co-administration with strong CYP3A inducers (e.g., rifampicin, carbamazepine, phenytoin, and St. John's wort) with sparsentan is not recommended. Co-administration with a moderate CYP3A inducer (e.g., efavirenz, dexamethasone, and phenobarbital) should be done with caution. When corticosteroid therapy is required, agents with no known or minimal *in vivo* CYP3A induction potential (e.g., budesonide, prednisone, prednisolone, methylprednisolone) are recommended.

Gastric acid reducing agents

Based on population pharmacokinetic (PK) analysis, concomitant use of an acid-reducing agent during sparsentan treatment would not have a statistically significant impact on the variability of sparsentan PK. Gastric pH modifying agents such as antacids, proton-pump inhibitors, and histamine 2 receptor antagonists can be used concomitantly with sparsentan.

Effect of sparsentan on other medicinal products

CYP Enyzmes

In vivo, sparsentan both inhibited and induced CYP3A4 and induced CYP2B6, CYP2C9 and CYP2C19.

Sparsentan is both a moderate inhibitor and an inducer of CYP3A4. *In vivo*, co-administration of single dose of 800 mg sparsentan with CYP3A4 substrate (midazolam) increased midazolam C_{max} by 1.4-fold and $AUC_{0\text{-}inf}$ by 1.6-fold. Co-administration of multiple doses of 800 mg sparsentan with CYP3A4 substrate (midazolam) had no effect on the systemic exposure of midazolam. Caution is advised when initiating sparsentan treatment with medicinal products metabolized by CYP3A4 (e.g., alfentanil, conivaptan, indinavir, simvastatin). If co-administration is unavoidable, especially with CYP3A4 substrates with a narrow therapeutic index (e.g., cyclosporine, fentanyl and tacrolimus), patients should be monitored for adverse reactions and dose of these substrates may need to be adjusted.

Sparsentan is a weak inducer of CYP2B6. *In vivo*, co-administration of multiple doses of 800 mg sparsentan with the CYP2B6 substrate (bupropion) decreased bupropion C_{max} by 32% and $AUC_{0\text{-}inf}$ by 33%. No dose adjustment is needed for drugs mainly metabolized by CYP2B6. However, caution is advised when co-administering sparsentan with narrow therapeutic index CYP2B6 substrates (e.g., efavirenz), as it may lower their plasma levels.

Sparsentan is a weak inducer of CYP2C9. *In vivo*, co-administration of multiple doses of 800 mg sparsentan with CYP2C9 substrate (tolbutamide) decreased tolbutamide C_{max} by 9% and $AUC_{0\text{-}inf}$ by 25%. No dose adjustment is needed for drugs mainly metabolized by CYP2C9. However, caution is advised when co-administering sparsentan with narrow therapeutic index CYP2C9 substrates (e.g., coumarin, warfarin, phenytoin), as sparsentan may lower their plasma levels.

Sparsentan is a moderate inducer of CYP2C19. *In vivo*, co-administration of multiple doses of 800 mg sparsentan decreased CYP2C19 substrate (omeprazole) C_{max} by 49% and $AUC_{0\text{-}inf}$ by 60% suggesting sparsentan is a moderate inducer of CYP2C19. Use CYP2C19 substrates with caution, as sparsentan may lower their plasma levels potentially resulting in subtherapeutic levels. If co-administration of sparsentan,

especially with narrow therapeutic index drugs (e.g., S-mephenytoin, diazepam), is necessary, dose of these substrates may need to be adjusted.

Transporters

Sparsentan is a weak inhibitor of P-gp. *In vivo*, co-administration of multiple doses of 800 mg sparsentan increased P-gp substrate (digoxin) C_{max} by 1.6-fold and $AUC_{0\text{-}inf}$ by 1.2-fold. Sparsentan may increase plasma levels of P-gp substrates. Patients should be monitored for adverse reactions when sparsentan is used with narrow therapeutic index drugs (e.g., dabigatran), and dose of these substrates may need to be adjusted.

Co-administration of multiple doses of 800 mg sparsentan increased rosuvastatin (a BCRP substrate) C_{max} by 1.6-fold and decreased $AUC_{0\text{-}inf}$ by 5% suggesting sparsentan doesn't affect the bioavailability of BCRP substrates. The complexity of BCRP-regulated transport processes in numerous different tissues may have resulted in the observed neutral net effect on AUC.

Administration of sparsentan had no effect on serum creatinine (a substrate of OAT2, OCT2, MATE1, and MATE2K), 6-beta-hydroxycortisol (a substrate of OAT3), or serum bile acid (a substrate of BSEP) levels.

Co-administration of 800 mg sparsentan decreased pitavastatin (a substrate of OATP1B1 and OATP1B3) C_{max} by 19% and $AUC_{0\text{-}inf}$ by 30% suggesting sparsentan is not an inhibitor of OATP1B1 and OATP1B3.

No dose adjustment is required when combining sparsentan with BCRP, OAT2, OCT2, MATE1, MATE2K, OAT3, BSEP, OATP1B1 and OATP1B3 substrate.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Sparsentan treatment must only be initiated in women of childbearing potential when the absence of pregnancy has been verified. Exclude pregnancy before, during and for 1 month after treatment with sparsentan has stopped. The frequency of recommended pregnancy testing should be determined by the method of contraception used and the associated likelihood of contraceptive failure. Women of childbearing potential have to use effective contraception during and up to 1 month after treatment has stopped.

Pregnancy

There are no or limited amount of data from the use of sparsentan in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Filspari is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Physicochemical data suggest excretion of sparsentan in human milk. A risk to newborns/infants cannot be excluded. Sparsentan should not be used during breastfeeding.

Fertility

There are no data on the effects of sparsentan on human fertility. Animal data did not indicate any impairment of male or female fertility (see section 5.3).

Fertility

There are no data on the effects of sparsentan on human fertility. Animal data did not indicate any impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Filspari may have minor influence on the ability to drive and use machines.
No studies on the effects of sparsentan on the ability to drive and use machines have been performed. It should, however, be taken into account that dizziness may occur when taking sparsentan (see section 4.8). Patients with dizziness, should be advised to refrain from driving or using machines until symptoms have subsided.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) were hypotension (10.8 %), hyperkalaemia (9.6 %), dizziness (7.8 %), and oedema peripheral (5.4 %). The most common serious adverse reaction reported was acute kidney injury (0.9 %).

Tabulated list of adverse reactions

The adverse reactions reported in the active-controlled phase 2 and phase 3 clinical trials in patients exposed to sparsentan in chronic kidney disease population including IgAN and FSGS (N=446) are listed in the table below by MedDRA system organ class and frequency convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000).

Table 1: Adverse drug reactions observed during clinical trials

System organ class	**Very common**	**Common**	**Uncommon**
Blood and lymphatic system disorders		-	Anaemia

System organ class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Hyperkalaemia	-
Nervous system disorders		Dizziness Headache	-
Vascular disorders	Hypotension	Orthostatic hypotension	-
Renal and urinary disorders		Renal impairment Acute kidney injury	-
General disorders and administration site conditions		Oedema peripheral Fatigue	-
Investigations		Blood creatinine increased Elevated transaminase[a]	-

[a] Elevated transaminase includes preferred terms of alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, and hepatic enzyme increased.

Description of selected adverse reactions

Haemoglobin decrease
In PROTECT, anaemia or decreased haemoglobin was reported as an ADR in 2 (1 %) subjects treated with sparsentan compared to 4 (2 %) irbesartan-treated subjects. Overall, haemoglobin ≤ 9 g/dL was reported at any time post treatment in 7 (3 %) subjects in the sparsentan treatment arm and 4 (2 %) subjects in the irbesartan treatment arm. This decrease is thought to be in part due to haemodilution. There were no treatment discontinuations due to anaemia.

Hepatic associated adverse events

In PROTECT, a total of 6 (3 %) subjects in the sparsentan group and 4 (2 %) subjects in the irbesartan group had elevation of liver transaminases exceeding 3 times upper-limit-of-normal without elevation of total bilirubin, after receiving study medication for 168 to 407 days, respectively. All events were non-serious and asymptomatic, the majority were mild or moderate in intensity, all were reversible, and other reasons have been identified as potential causal factors or as potentially contributing to transaminase elevations. No clinical symptoms of hepatic injury were observed. In the sparsentan group, the study drug was discontinued in 3 subjects after positive rechallenge while in 2 subjects sparsentan treatment, was restarted with no repeated hepatic enzyme elevations.

Acute kidney injury (AKI)

In PROTECT, acute kidney injury ADRs were reported in 4 (2%) subjects in the sparsentan group and 3 (1%) subjects in the irbesartan group. Four subjects (2%) who received sparsentan reported serious AKI all of which were reversible. None of the serious AKI required dialysis. In the sparsentan group, the study drug was discontinued in 3 subjects.

Hyperkalaemia

In PROTECT, hyperkalaemia was reported as an ADR in 20 (10 %) subjects treated with sparsentan compared to 16 (8 %) irbesartan-treated subjects. All events were non-serious in subjects treated with sparsentan, the majority were mild to moderate in intensity and all were reversible. There were no treatment discontinuations due to hyperkalaemia. The risk of hyperkalaemia is increasing for patients with a lower eGFR.

Hypotension

Hypotension was reported during treatment with sparsentan. In PROTECT, a SBP ≤ 100 mmHg or a reduction in SBP exceeding 30 mmHg, was reported in 12 % and 10 % of patients on sparsentan, respectively, versus 11 % and 10 % on irbesartan. In subjects treated with sparsentan only 15 subjects (7.4 %) were ≥ 65 years old. Hypotension was reported in 20 (11 %) subjects < 65 years of age and in 6 (40 %) subjects 65 to 74 years of age.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

4.9 Overdose

Sparsentan has been administered in doses of up to 1600 mg/day in healthy subjects without evidence of dose limiting toxicities. Patients who experience overdose (possibly experiencing signs and symptoms of hypotension) should be monitored closely and appropriate symptomatic treatment given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: agents acting on the renin-angiotensin system, ATC code: C09XX01

Mechanism of action

Sparsentan is a dual endothelin angiotensin receptor antagonist.

It is a single molecule that functions as a high affinity, dual-acting antagonist of both the ET_AR and AT_1R. Endothelin 1, via ET_AR, and angiotensin II, via AT_1R, mediate processes that lead to IgAN progression through haemodynamic actions and mesangial cell proliferation, increased expression and activity of proinflammatory and profibrotic mediators, podocyte injury, and oxidative stress. Sparsentan inhibits activation of both ET_AR and AT_1R and thereby reduces proteinuria and slows the progression of kidney disease.

Pharmacodynamic effects

In a randomised, positive- and placebo-controlled study with healthy subjects, sparsentan caused mild QTcF prolongation with a peak effect of 8.8 ms (90 % CI: 5.9, 11.8) at 800 mg and 8.1 ms (5.2, 11.0) at 1600 mg. In an additional study with healthy subjects, at sparsentan exposure exceeding exposure at maximum recommended human dose by more than 2-fold, the peak effect was 8.3 (6.69, 9.90) ms. Therefore, it is unlikely that sparsentan has a clinically relevant effect on QT prolongation.

Clinical efficacy and safety

The efficacy and safety of sparsentan, a non-immunossupressive drug, has been evaluated in PROTECT in patients with IgAN.

PROTECT is a randomised, double-blind (110 weeks), active-controlled, multicentre, global phase 3 trial in patients with IgAN. The trial enrolled patients aged ≥ 18 years, including 15 (7.4 %) sparsentan-treated patients aged ≥ 65 years, with an eGFR ≥ 30 mL/min/1.73 m^2 and total urine protein excretion ≥ 1.0 g/day. Prior to enrolment, patients were on the maximum tolerated dose of an ACE inhibitor and/or an ARB for at least 3 months. The ACE inhibitors and/or ARB therapy were discontinued prior to initiation of sparsentan. Patients with a baseline potassium value exceeding 5.5 mmol/L were excluded.

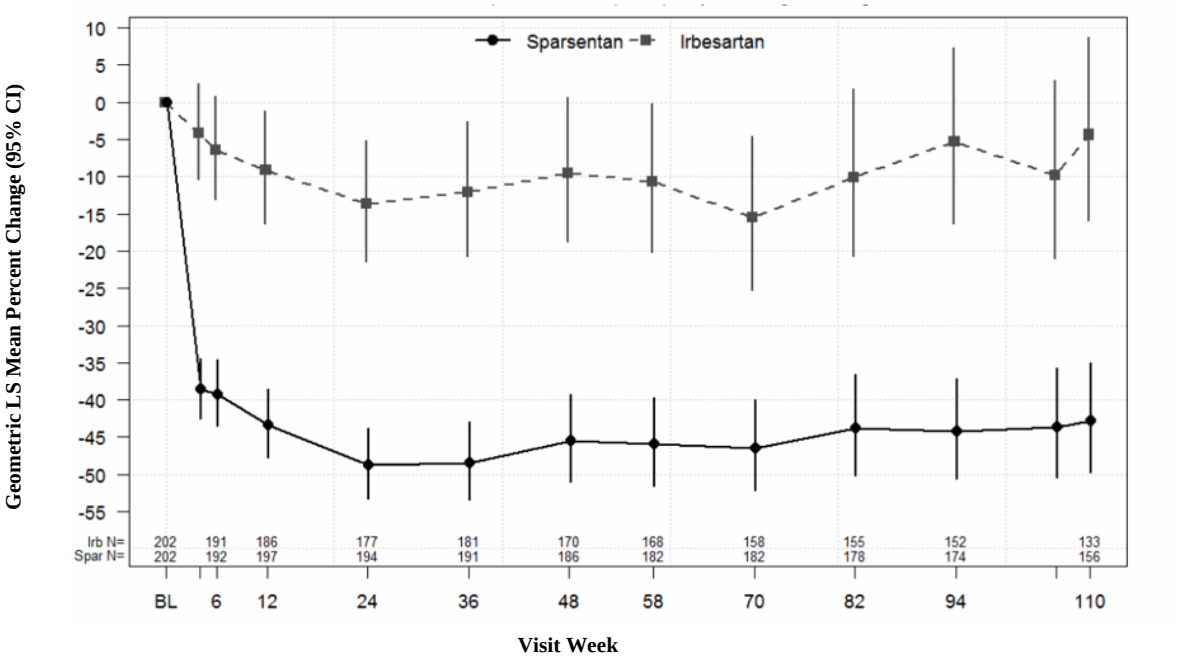
A total of 404 patients were randomised and received sparsentan (n = 202) or irbesartan (n = 202). Treatment was initiated with sparsentan at 200 mg once daily or irbesartan 150 mg once daily. After 14 days, the dose was to be titrated, as tolerated, to the recommended dose of sparsentan 400 mg once daily or irbesartan 300 mg once daily. Dose tolerance was defined as systolic blood pressure > 100 mmHg and diastolic blood pressure > 60 mmHg after 2 weeks and no AEs (e.g, worsening oedema) or laboratory findings (e.g, serum potassium > 5.5 mEq/L [5.5 mmol/L]). Inhibitors of the RAAS or endothelin system were prohibited during the trial. Other classes of antihypertensive agents were permitted as needed to achieve target blood pressure. Treatment with immunosuppressive agents was permitted during the trial at the discretion of the investigator.

Baseline characteristics for eGFR and proteinuria were comparable between treatment groups. The overall population had a mean (SD) eGFR of 57 (24) mL/min/1.73 m^2 and a median urine protein/creatinine (UP/C) ratio of 1.24 g/g

(interquartile range: 0.83, 1.77). The mean age was 46 years (range 18 to 76 years); 70 % were male, 67 % White, 28 % Asian, 1 % Black or African American, and 3 % were other race.

The primary analysis of proteinuria was conducted after 36 weeks following randomization of approximately 280 subjects, to determine whether the treatment effect of the primary efficacy endpoint, the change from baseline in UP/C at week 36, is statistically significant. The trial met its primary endpoint, which was change from baseline in the UP/C ratio at week 36. Geometric mean UP/C at week 36 was 0.62 g/g in the sparsentan arm versus 1.07 g/g in the irbesartan arm. The geometric least squares mean percent change in UP/C from baseline at week 36 was -49.8 % (95 % confidence interval [CI]: -54.98, -43.95) in the sparsentan arm versus -15.1 % (95 % CI: -23.72, -5.39) in the irbesartan arm ($p < 0.0001$). At the final analysis, sparsentan demonstrated a rapid and durable antiproteinuric treatment effect over 2 years, with a geometric mean UP/C at week 110 of 0.64 g/g in the sparsentan arm versus 1.09 g/g in the irbesartan arm representing a 42.8 % mean reduction from baseline (95 % CI: -49.75, -34.97) compared to only 4.4 % for irbesartan (95 % CI: -15.84, 8.70). Improvement in proteinuria reduction was consistently observed with sparsentan as early as 4 weeks and sustained through week 110 (Figure 1).

Figure 1: Percent change from baseline urine protein/creatinine ratio by visit (PROTECT)



Notes: Adjusted geometric least squares mean ratio of UP/C relative to baseline was based on a longitudinal repeated measures model stratified by screening eGFR and proteinuria, reported as percentage change along with the respective 95 % CI. Analysis includes UP/C data during the double-blind period from all patients who were randomised and received at least 1 dose of study medication. Baseline was defined as the last non-missing observation prior to and including the start of dosing.

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least squares; UP/C = urine protein/creatinine ratio.

Estimated GFR

At the time of confirmatory analysis, the improvement in 2 year eGFR chronic slope (from 6 weeks onwards) was 1.1 mL/min/1.73 m^2 per year with sparsentan compared to irbesartan (95 % CI: 0.07, 2.12; p = 0.037), and the corresponding improvement in 2 year eGFR total slope (from baseline onwards) was 1.0 mL/min/1.73 m^2 per year (95 % CI: -0.03, 1.94; p = 0.058). The absolute change from baseline in eGFR at 2 years was -5.8 mL/min/1.73 m2 (95 % CI: -7.38, -4.24) for sparsentan compared to -9.5 mL/min/1.73 m^2 (95 % CI: -11.17, -7.89) for irbesartan.

To address an imbalance in intercurrent events between the sparsentan and irbesartan groups, a post-hoc analysis was conducted including all observed data after treatment discontinuation or initiation of rescue immunosuppressive therapy. The improvement in 2 year eGFR chronic slope (from 6 weeks onwards) was 1.3 mL/min/1.73 m2 per year in favor of sparsentan compared to irbesartan (95 % CI: 0.33,2.31; p = 0.0087), and the corresponding improvement in 2 year eGFR total slope (from baseline onwards) was 1.2 mL/min/1.73 m2 per year (95 % CI: 0.21,2.13; p = 0.0168). The absolute change from baseline in eGFR at 2 years was -6.1 mL/min/1.73 m2 (95 % CI: -7.65, -4.54) for sparsentan compared to -9.9 mL/min/1.73 m2 (95 % CI: -11.54, -8.31) for irbesartan.

Additional information

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy. ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

<u>Paediatric population</u>

The licensing authority has deferred the obligation to submit the results of studies with Filspari in one or more subsets of the paediatric population in the treatment of immunoglobulin A nephropathy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single oral dose of 400 mg sparsentan, the median time to peak plasma concentration is approximately 3 hours.

Following a single oral dose of 400 mg sparsentan, the geometric mean C_{max} and AUC are 6.97 μg/mL and 83 μg × h/mL, respectively. Steady-state plasma levels are reached within 7 days with no accumulation of exposure at the recommended dosage.

Following a dose of 400 mg sparsentan daily, the steady-state geometric mean C_{max} and AUC are 6.47 μg/mL and 63.6 μg × h/mL, respectively.

Food effect
At doses of 400 mg and below, the effect of a high fat meal on sparsentan exposure was not clinically relevant. Sparsentan can be taken with or without food.

Distribution

Based on population pharmacokinetic analysis, the apparent volume of distribution at steady state is 61.4 L.

Sparsentan is highly bound (> 99 %) to human plasma proteins with preferential binding to albumin and moderate binding to α1-acid glycoprotein.

Biotransformation

Sparsentan is primarily metabolised by CYP3A4 with a minor contribution of CYP2C8, 2C9 and 3A5. Parent compound is the predominant entity in human plasma, representing approximately 90% of the total radioactivity in circulation. A minor hydroxylated metabolite was the only metabolite in plasma that accounted for >1% of the total radioactivity (approximately 3 %). The main metabolic pathway of sparsentan was oxidation and dealkylation, and 9 metabolites were identified in human faeces, plasma and urine.

Elimination

The clearance of sparsentan is time dependent. Based on population pharmacokinetic analysis, the apparent clearance is 3.88 L/h, increasing to 5.11 L/h at steady state.

The half-life of sparsentan at steady state is estimated to be 9.6 hours.

Following a single 400 mg dose of radiolabelled sparsentan, 82 % of the dosed radioactivity was recovered within a 10 day collection period: 80 % via the faeces with 9 % as unchanged, and 2 % via the urine with a negligible amount as unchanged.

Linearity/non-linearity

The C_{max} and AUC of sparsentan increase less than proportionally following administration of single doses of 200 mg to 1600 mg. Sparsentan showed time-dependent pharmacokinetics with no C_{max} accumulation and decreased AUC at steady state following a dose of 400 or 800 mg daily.

Special populations

Elderly

Population pharmacokinetic analysis found no significant effect of age on the plasma exposure of sparsentan. No dosage adjustment is necessary for elderly patients (see section 4.2). Sparsentan has not been studied in patients >75 years of age.

Hepatic impairment

In a dedicated hepatic impairment study, systemic exposure following a single dose of 400 mg sparsentan was similar in patients with baseline mild or moderate hepatic impairment (Child-Pugh A or Child-Pugh B classification) compared to patients with normal hepatic function. No dose adjustment is required in patients with mild or moderate hepatic impairment. Sparsentan should be used with caution in patients with moderate hepatic impairment (see sections 4.2 and 4.4).

No data are available in patients with severe hepatic impairment and sparsentan is therefore not recommended in these patients (Child-Pugh C classification) (see section 4.2).

Renal impairment

Based on population pharmacokinetic analysis in chronic kidney disease patients with mild (creatinine clearance 60 to 89 mL/min), moderate (creatinine clearance 30 to 59 mL/min), and severe (creatinine clearance 15 to 29 mL/min) kidney disease, there is no clinically meaningful effect of kidney impairment on pharmacokinetics as compared to normal kidney function (creatinine clearance ≥ 90 mL/min). No data are available in patients with end-stage kidney disease (creatinine clearance < 15 mL/min).

Based on limited available data, no dose adjustment can be recommended for patients with severe kidney disease (eGFR < 30 mL/min/1.73 m^2, see section 4.2). Sparsentan has not been studied in patients with severe kidney disease or undergoing dialysis, therefore sparsentan is not recommended in these patients. Sparsentan has not been studied in patients who have received a kidney transplant, therefore in this patient population sparsentan should be used with caution (see section 4.2).

Other special populations

Population pharmacokinetic analyses indicate that there is no clinically meaningful effect of age, gender, or race on the pharmacokinetics of sparsentan.

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, toxicity to reproduction, and juvenile development.

Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In embryo-foetal development studies in rat and rabbit, developmental toxicity was seen in both species. In rats, dose-dependent teratogenic effects in the form of craniofacial malformations, skeletal abnormalities, increased embryo-foetal lethality, and reduced foetal weights were observed at all doses of sparsentan tested at exposures 8-fold and 13-fold over the AUC for 800 mg/day and 400 mg/day in humans. In rabbits, there were no foetal malformations or effects on embryo-foetal viability or foetal growth, but an increase in skeletal variations (supernumerary cervical ribs) occurred at an exposure of approximately 0.10 and 0.2 times the AUC in humans at 800 mg/day and 400 mg/day.

In the pre- and postnatal development study in rat, maternal toxicity including death was seen at ~8-fold and 13-fold, and maternal toxicity at ~2-fold and 3-fold the AUC in humans at 800 mg/day and 400 mg/day. An increase in pup deaths and decreased growth occurred at ~8-fold and 13-fold, and decreased growth at ~2-fold and 3-fold the AUC in humans at 800 mg/day and 400 mg/day.

Juvenile animal studies

Juvenile animal studies in rats demonstrated that there were no general toxicological adverse effects seen up to 10 mg/kg/day and no reproductive toxicity in males or females up to 60 mg/kg/day when dosing started on postnatal day (PND) 14 (equivalent to 1-year-old children). Vascular toxicity occurred at doses ≥3 mg/kg/day when dosing started on PND 7 (equivalent to newborn infants).

Environmental risk assessment (ERA)

Conclusions of studies for sparsentan show that sparsentan is considered not to be persistent, bioaccumulative and toxic (PBT) nor very persistent and very

bioaccumulative (vPvB). A risk to the sewage treatment plant, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of sparsentan (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Lactose
Sodium starch glycolate (type A)
Colloidal anhydrous silica
Magnesium stearate

Film coating

Poly(vinyl alcohol)
Macrogol
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with child-resistant polypropylene cap.

Pack size of 30 film-coated tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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92042 Paris La Défense Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15240/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/11/2024

10 DATE OF REVISION OF THE TEXT

20/01/2026