swissmedic

Date: 3 December 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Filspari

International non-proprietary name: sparsentan

Pharmaceutical form: film-coated tablets

Dosage strength(s): 200 mg, 400 mg

Route(s) of administration: oral

Marketing authorisation holder: Vifor (International) Inc.

Marketing authorisation no.: 69241

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 14 October 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgAN	Immunoglobulin A nephropathy
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for sparsentan in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 21 March 2023.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urinary protein excretion > 1.0 g/day (or a urinary protein-to-creatinine ratio ≥ 0.75 g/g

2.2.2 Approved indication

Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urinary protein excretion of ≥1.0 g/day (or a urinary protein/creatinine quotient of ≥0.75 g/g) (see section "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

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.
The tablets should be swallowed whole with water to avoid a bitter taste. Filspari can be taken with or without food.

Special populations
Elderly
No dose adjustment is recommended in elderly patients.

Hepatic impairment
No dose adjustment in patients with mild or moderate hepatic impairment (Child-Pugh A or Child-Pugh B classification). There is limited clinical experience with moderate hepatic impairment.
Filspari is not recommended in patients with severe hepatic impairment (Child-Pugh C classification)
There is limited clinical experience with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) values more than 2 times the upper limit of the normal range (ULN).
Therefore, Filspari should not be initiated in patients with AST/ALT > 2 × ULN.

Renal impairment
No dose adjustment is required in patients with mild or moderate kidney disease.
Filspari is not recommended in patients with severe kidney disease or in patients undergoing dialysis.

In patients who have received a kidney transplant, Filspari should be used with caution.

Children and adolescents
The safety and efficacy of Filspari in children below the age of 18 years with IgAN have not yet been established.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	7 March 2024
Formal objection	11 March 2024
Response to formal objection	14 March 2024
Formal control completed	19 March 2024
Preliminary decision	29 May 2024
Response to preliminary decision	8 August 2024
Labelling corrections	28 August 2024
Response to labelling corrections	24 September 2024
Final decision	14 October 2024
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the European Medicines Agency (EMA). This SwissPAR relates to the publicly available EMA assessment report for Filspari, published 28 May 2024, Procedure No. EMEA/H/C/005783/0000.

3 Medical context

Sparsentan is a dual receptor antagonist for endothelin type A receptor (ET_AR) and the angiotensin II receptor type 1 (AT_1R). Endothelin 1 (ET-1) and angiotensin II (Ang II) are vasoactive peptides that affect renal haemodynamics and promote other factors thought to be involved in the pathogenesis of IgAN (e.g., cell growth, oxidative stress, expression, and activity of proinflammatory and profibrotic mediators).

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). The SwissPAR relating to quality aspects refers to the publicly available EMA assessment report for Filspari, published 28 May 2024, Procedure No. EMEA/H/C/005783/0000.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). The nonclinical aspects in this SwissPAR refer to the publicly available EMA assessment report for Filspari, published 28 May 2024, Procedure No. EMEA/H/C/005783/0000 .

6 Clinical aspects

Swissmedic has only assessed parts of the primary data submitted with this application and principally relies on the assessment of the foreign reference authority, the European Medicines Agency (EMA). With regard to the clinical aspects, the SwissPAR refers to the publicly available EMA assessment report for Filspari, published 28 May 2024, Procedure No. EMEA/H/C/005783/0000.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Filspari was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report suspected new or serious adverse reactions. See section "Undesirable effects" for how to report adverse reactions.
Filspari is authorised for a limited period of time, see section ‘Indications/Possible uses’.

FILSPARI

Composition

Active substances

sparsentan

Excipients

Tablet core: silicified microcrystalline cellulose, lactose, carboxymethyl starch sodium (type A), highly dispersed silicon dioxide, magnesium stearate

Film-coating: Poly(vinyl alcohol), macrogol 3350, talc, titanium dioxide (E171)

200 mg film-coated tablets: 1 film-coated tablet contains 42 mg lactose and max. 0.9 mg sodium.
400 mg film-coated tablets: 1 film-coated tablet contains 84 mg lactose and max. 1.8 mg sodium.

Pharmaceutical form and active substance quantity per unit

Film-coated tablet

Amount of active substance per unit
200 mg film-coated tablets: Each tablet contains 200 mg sparsentan.
400 mg film-coated tablets: Each tablet contains 400 mg sparsentan.

Appearance
200 mg film-coated tablets: White to cream-coloured, oval film-coated tablet with “105” embossed on one side, the other side of the tablet has no embossing. The tablets are approx. 13 mm long and approx. 7 mm wide.

400 mg film-coated tablets: White to cream-coloured, oval film-coated tablet with “021” embossed on one side, the other side of the tablet has no embossing. The tablets are approx. 18 mm long and approx. 8 mm wide.

Indications/Uses

Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urinary protein excretion of ≥1.0 g/day (or a urinary protein/creatinine quotient of ≥0.75 g/g) (see section “Clinical efficacy”).

Due to an incomplete clinical data situation at the time of the review of the application, this indication is authorised for a limited period (Art. 9a Therapeutic Products Act). The temporary authorisation is subject to the timely fulfilment of conditions. Once these have been fulfilled, the temporary authorisation can be converted into a full authorisation.

Dosage/Administration

Usual dosage
Treatment with Filspari should be started with a dose of 200 mg once daily over a period of 14 days and then increased to a maintenance dose of 400 mg once daily depending on tolerability.

For titration of the initial dose of 200 mg once daily to the maintenance dose of 400 mg once daily, 200 mg film-coated tablets and 400 mg are available to reach the maintenance dose.
In patients with tolerability problems (systolic blood pressure [SBP] ≤100 mmHg, diastolic blood pressure ≤60 mmHg, worsening oedema or hyperkalaemia), an adjustment of concomitant medication followed by a temporary dose reduction or discontinuation of Filspari is recommended (see "Warnings and precautions" and “Clinical efficacy”).
If treatment with Filspari is restarted after an interruption, consideration should be given to repeating the original dosing regimen. If hypotension or changes in liver function persist, treatment interruption with or without prior dose reduction of Filspari may be considered (see "Warnings and precautions").

Missed doses
If a dose is missed, this dose should be omitted and the next dose taken at the scheduled time. No double or additional doses should be taken.

Elderly patients
No dose adjustment is recommended in elderly patients (see "Pharmacokinetics"). In elderly patients, treatment with Filspari should be started with a dose of 200 mg once daily over a period of 14 days. The increase to a maintenance dose of 400 mg daily should be carried out with caution depending on tolerability (see "Warnings and precautions").

Patients with hepatic impairment
Based on pharmacokinetic data, no dose adjustment of Filspari is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A or Child-Pugh B) keine Dosisanpassung von Filspari erforderlich (see "Pharmacokinetics").

There is only limited clinical experience with moderate hepatic impairment. Therefore, Filspari should be used with caution in these patients (see "Warnings and precautions").

Filspari 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) levels greater than 2 times the upper limit of normal (ULN). Therefore, Filspari should not be started in patients with AST/ALT >2 × ULN (see "Warnings and precautions").

Patients with 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 "Pharmacokinetics"). As there is limited clinical experience in patients with severe kidney disease, Filspari is not recommended for use in these patients (see "Warnings and precautions").
Filspari has not been studied in patients who have received a kidney transplant. Filspari should therefore be used with caution in these patients.
Filspari has not been studied in dialysis patients. The initiation of treatment with Filspari is not recommended in these patients.

Children and adolescents
The safety and efficacy of Filspari in children under 18 years of age has not yet been established. No data are available.

Method of administration

For oral use.

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

Contraindications

- Hypersensitivity to the active substance or to any of the other ingredients (see "Composition").
- Pregnancy (see "Warnings and precautions" and "Pregnancy, lactation")
- Concomitant administration of angiotensin receptor blockers (ARB), endothelin receptor antagonists (ERA) or renin inhibitors (see “Warnings and precautions” and “Interactions”)

Warnings and precautions

Women of childbearing potential
Treatment with Filspari may only be started in women of childbearing potential if it is ensured that there is no pregnancy and effective contraception is used (see "Contraindications" and "Pregnancy, lactation").

Hypotension
Hypotension has been associated with the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, including Filspari. Hypotension may occur during treatment with Filspari and has been reported most frequently in elderly patients (see "Undesirable effects").

In patients at risk of hypotension, consideration should be given to omitting or adjusting other antihypertensives and maintaining an adequate volume status. If hypotension develops despite omission or reduction of other antihypertensives, dose reduction or interruption of Filspari should be considered. A transient hypotensive reaction is not a contraindication to the continued administration of Filspari. Treatment can be resumed as soon as blood pressure has stabilised.

If hypotension persists despite discontinuation or reduction of antihypertensives, the dosage of Filspari should be reduced to the original starting dose until blood pressure stabilises. A dose interruption in treatment with Filspari should be considered if symptoms of hypotension persist after a 2-week dose reduction. Filspari should be used with caution in patients with systolic blood pressure values ≤100 mmHg (see "Dosage/administration"). The dose of Filspari should not be increased in patients with systolic blood pressure values ≤100 mmHg (see "Dosage/Administration").

Renal impairment
A transient increase in serum creatinine has been associated with RAAS inhibitors, including Filspari. A transient increase in serum creatinine may occur, particularly at the start of treatment with Filspari (see "Undesirable effects"). Serum creatinine and serum potassium levels should be monitored regularly in patients at risk. Filspari should be used with caution in patients with bilateral stenosis of the renal artery.

Due to the limited clinical experience in patients with an eGFR <30 ml/min/1.73 m^2, Filspari is not recommended for use in these patients (see "Dosage/Administration").

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 treatment with Filspari (see "Undesirable effects").

If fluid retention develops during treatment with Filspari, treatment with diuretics is recommended or the dose of existing diuretics should be increased before changing the dose of Filspari. Treatment with diuretics may be considered in patients who have been diagnosed with fluid retention before starting treatment with Filspari.

Filspari has not been studied in patients with heart failure. Filspari should therefore be used with caution in patients with heart failure.

Liver function

Increases in ALT or AST levels of at least 3 × ULN have been observed during treatment with Filspari (see “Undesirable effects”).

No concomitant increases in bilirubin >2 × ULN or cases of liver failure have been observed in patients treated with Filspari. Therefore, to reduce the risk of potential severe liver toxicity, serum aminotransferase levels and total bilirubin should be monitored before starting treatment and then monitoring should be continued every three months.

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

Re-administration of Filspari should only be considered if liver enzyme levels and bilirubin return to pre-treatment baseline levels and only in patients without clinical symptoms of liver toxicity. Filspari should not be used in patients with elevated aminotransferases (>2 × ULN) before starting treatment (see "Dosage/Administration").

There is only limited clinical experience with moderate hepatic impairment. Filspari should therefore be used with caution in these patients (see “Dosage/Administration”).

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 renal impairment (including acute renal failure). Dual blockade of the RAAS by combined use of ACE

inhibitors and angiotensin II receptor blockers (partly a mechanism of sparsentan) or renin inhibitors is therefore not recommended (see “Interactions” and “Clinical efficacy”). If dual blockade treatment is considered essential, it should only be carried out under the supervision of a specialist and with frequent close monitoring of renal function, electrolytes and blood pressure.

Hyperkalaemia
Treatment should not be started in patients with a serum potassium level >5.5 mmol/l. As with other medical devices that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during treatment with Filspari, especially in the presence of renal impairment and/or heart failure. Close monitoring of serum potassium is recommended in patients at risk. If clinically significant hyperkalaemia occurs in patients, adjustment of concomitant medication, temporary dose reduction or discontinuation is recommended. If serum potassium is >5.5 mmol/l, discontinuation should be considered.

Patients with the rare hereditary galactose intolerance, complete lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Interactions

Concomitant use with ARBs, ERAs and renin inhibitors
The concomitant use of sparsentan with ERA such as bosentan, ambrisentan, macitentan, sitaxentan, ARB such as irbesartan, losartan, varsartan, candesartan, telmisartan or renin inhibitors such as aliskiren is contraindicated (see “Contraindications”).

Concomitant use with ACE and mineral corticoid (aldosterone) receptor inhibitors
The concomitant administration of sparsentan with mineralocorticoid (aldosterone) receptor inhibitors such as spironolactone and finerenone is likely to be associated with an increased risk of hyperkalaemia.

No data are available on the combination of sparsentan with ACE inhibitors such as enalapril or lisinopril. Data from clinical studies have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) by the combined use of ACE inhibitors and angiotensin II receptor blockers or aliskiren is associated with a higher incidence of adverse events such as hypotension, hyperkalaemia and impaired renal function (including acute renal failure) compared to the use of a single agent targeting the RAAS (see “Pharmacokinetics”).

The use of sparsentan in combination with ACE inhibitors such as enalapril or lisinopril should be used with caution and blood pressure, potassium levels and renal function should be monitored (see "Warnings and precautions").

Concomitant use with potassium preparations and potassium-sparing diuretics
As hyperkalaemia may occur in patients treated with medicinal products that antagonise the angiotensin II receptor type 1 (AT1R) (see "Undesirable effects"), the concomitant use of potassium preparations, potassium-sparing diuretics such as spironolactone, eplerenone, triamterene or amiloride or potassium-containing salt substitutes may increase the risk of hyperkalaemia and is not recommended.

Effects of other medicinal products on sparsentan
Sparsentan is mainly metabolised by cytochrome P450 (CYP)3A.

Strong and moderate CYP3A inhibitors
Co-administration of sparsentan with itraconazole (strong CYP3A inhibitor) increased the C_{max} of sparsentan by 1.3-fold and the $AUC_{0\text{-}inf}$ 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.

Co-administration of sparsentan with cyclosporine (moderate CYP3A inhibitor) increased the C_{max} of sparsentan by 1.4-fold and the $AUC_{0\text{-}inf}$ by 1.7-fold. Co-administration with a moderate CYP3A inhibitor such as conivaptan, fluconazole and nelfinavir should be done with caution.

CYP3A inducers
Sparsentan is a CYP3A substrate. Concomitant administration of a moderate or strong CYP3A inducer such as rifampicin, efavirenz, dexamethasone, carbamazepine, phenytoin and phenobarbital will reduce the exposure of sparsentan, which could affect the efficacy of sparsentan. Concomitant administration with a moderate or strong CYP3A inducer is therefore not recommended.

Medicinal products to reduce gastric acidity
According to a population pharmacokinetic (PK) analysis, concomitant administration of an acid-reducing medicinal product during treatment with sparsentan would not have a significant effect on the variability of sparsentan PK. Medicinal products that alter the pH in the stomach, such as antacids, proton pump inhibitors and histamine-2 receptor agonists, can be used concomitantly with sparsentan.

Effects of sparsentan on other medicinal products

In vitro, CYP3A was inhibited and induced by sparsentan, while CYP2B6, CYP2C9 and CYP2C19 were induced.

Co-administration of sparsentan at Steady State with the CYP3A4 substrate midazolam had no effect on the systemic exposure of midazolam. Co-administration of sparsentan at steady state with the CYP2B6 substrate bupropion decreased both the C_{max} of bupropion and the $AUC_{0\text{-}inf}$ by 1.5-fold.

No dose adjustment is required when sparsentan is combined with a CYP3A4 or CYP2B6 substrate at steady state.

The significance of CYP2C9 and CYP2C19 induction by sparsentan has not been investigated in a clinical study. Co-administration of sparsentan with a CYP2C9 substrate such as S-warfarin, phenytoin and ibuprofen or CYP2C19 substrates such as omeprazole and phenytoin should be used with caution.

The significance of CYP3A4 induction following a single dose of sparsentan has not been investigated in a clinical study. Sparsentan is an inhibitor of CYP3A4 and may have an effect on the PK of medicinal products that are substrates of CYP3A4 when initiating treatment with sparsentan. Therefore, the start of treatment with sparsentan as concomitant medication with a CYP3A4 substrate, such as alfentanil, conivaptan, indinavir, cyclosporine and tacrolimus should be undertaken with caution.

In vitro, sparsentan is an inhibitor of P-gp, BCRP, OATP1B3 and OAT3 at relevant concentrations.

The significance of P-gp inhibition by sparsentan has not been investigated in a clinical study. Co-administration of sparsentan with P-gp inhibitory substrates should be used with caution if P-gp inhibition is known to have a significant effect on absorption.

Co-administration of sparsentan with pitavastatin (a substrate of OATP1B1, OATP1B3 and BCRP) decreased the C_{max} of pitavastatin by 1.2-fold and the $AUC_{0\text{-}inf}$ by 1.4-fold. No dose adjustment is required when sparsentan is combined with an OATP1B1, OATP1B3 or BCRP substrate.

No clinical study has been conducted to investigate the effect of sparsentan on a sensitive OAT3 substrate. However, at a dose of 800 mg, sparsentan appears to have no effect on the biomarker 6β-hydroxycortisol (substrate of OAT3), suggesting that the clinical effect is most likely limited.

Pregnancy, lactation

Women of childbearing potential

Treatment with Filspari may only be started in women of childbearing potential if it is certain that they are not pregnant. Women of childbearing potential should use a reliable method of contraception during treatment and for up to one month after the end of treatment.

Pregnancy

To date, there is no or only very limited experience with the use of Filspari in pregnant women. Animal studies have shown reproductive toxicity (see "Preclinical data").

Filspari is contraindicated during pregnancy (see “Contraindications”).

Breast-feeding

Physicochemical data indicate excretion of sparsentan in human milk. A risk for newborns/infants cannot be excluded. Filspari should not be used during breastfeeding.

Fertility

No data are available on the effects of sparsentan on fertility in humans. Experimental animal data did not indicate any impairment of male or female fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Filspari may have a minor effect on the ability to drive and use machines.
No studies have been conducted on the effects of Filspari on the ability to drive and use machines. However, it should be noted that dizziness may occur when taking Filspari (see “Undesirable effects”). Patients with dizziness should be advised to refrain from driving or using machines until the symptoms have subsided.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) were hypotension (9%), hyperkalaemia (7%), dizziness (7%) and peripheral oedema (5%). The most frequently reported serious adverse reaction was acute kidney injury (1%).

List of adverse reactions

Supportive safety data were obtained from 27 clinical trials involving more than 500 patients receiving Filspari for chronic kidney disease, including IgAN (see “Clinical efficacy”).

The adverse reactions are ordered by MedDRA system organ class and frequency 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)

Table 1: Adverse reactions observed in clinical studies

System organ class	Common	Uncommon
Blood and lymphatic system disorders	-	Anaemia
Metabolism and nutrition disorders	Hyperkalaemia	-
Nervous system disorders	Dizziness Headache	-
Vascular disorders	Hypotension Orthostasis syndrome	-
Renal and urinary disorders	Renal impairment Acute kidney injury	-
General diseases and administration site conditions	Peripheral oedema Fatigue	-
Investigations	Elevated creatinine in blood Elevated transaminases[a]	-

[a] Elevated transaminases includes preferred terms such as elevated alanine aminotransferases, elevated aspartate aminotransferases, elevated gamma-glutamyltransferases, elevated liver enzymes and elevated transaminases.

Description of selected adverse reactions

Decreased haemoglobin

In PROTECT, anaemia or decreased haemoglobin was reported as an ADR in 2 (<1%) subjects treated with sparsentan compared to 2 (<1%) subjects treated with irbesartan. Overall, haemoglobin levels of ≤9 g/dl were reported in 5 (2.5%) subjects in the sparsentan treatment group and 3 (1.5%) subjects in the irbesartan treatment group at any time after treatment. It is assumed that this decrease is partly due to haemodilution. There were no treatment discontinuations due to anaemia.

Adverse reactions affecting the liver

In PROTECT, a total of 6 (3%) participants in the sparsentan group and 4 (2%) participants in the irbesartan group had elevated liver transaminase levels that exceeded the upper normal limit without elevation of total bilirubin by more than 3-fold after receiving the study drug for 168 to 407 days each. All events were non-serious and asymptomatic, mostly of mild or moderate intensity. All events were reversible and were identified as possible causative factors or as possibly contributing to the increase in transaminases, or as other causes. In the sparsentan group, the study drug was discontinued in 3 participants after positive rechallenge, while in 2 participants treatment with sparsentan was resumed without renewed elevation of liver enzymes.

Acute kidney injury (AKI)

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

Hyperkalaemia

In PROTECT, hyperkalaemia was reported as an ADR in 18 (9%) sparsentan-treated participants, compared to 16 (8%) participants in the irbesartan-treated group. In the sparsentan-treated participants, all events were non-serious and most were mild to moderate in intensity, all of which were reversible. There were no treatment discontinuations due to hyperkalaemia. The risk of hyperkalaemia increases in patients with a low eGFR.

Hypotension

In PROTECT, SBP <100 mmHg and a reduction in SBP of more than 30 mmHg were reported for 10% and 8% of sparsentan-treated patients, respectively, compared to 9% and 6% for irbesartan. Among the participants treated with sparsentan, only 15 participants (7.4%) were over 65 years of age. Hypotension was reported in 17 (9%) participants aged <65 years and in 5 (33%) participants aged 65 to 74 years.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Filspari has been administered to healthy individuals at doses up to 1600 mg/day with no evidence of dose-limiting toxicities. Patients who overdose (possibly with signs and symptoms of hypotension) should be carefully monitored and receive appropriate symptomatic treatment.

Properties/Effects

ATC code

C09XX01

Mechanism of action

Sparsentan is a dual endothelin angiotensin receptor antagonist.

It is a single molecule that acts as a high-affinity, dual-acting antagonist of both ET_AR and AT_1R. Endothelin-1 via ET_AR and angiotensin II via AT_1R mediate processes that lead to the progression of

IgAN through haemodynamic effects and mesangial cell proliferation, increased expression and activity of proinflammatory and profibrotic mediators, podocyte damage and oxidative stress. Sparsentan inhibits the activation of both ET_AR and AT_1R, thereby reducing proteinuria and slowing the progression of renal disease.

Pharmacodynamics

In a randomised positive- and placebo-controlled study with healthy participants, sparsentan caused a slight QTcF prolongation with a maximum effect of 8.8 ms (90% CI: 5.9; 11.8) at 800 mg and 8.1 ms (90% CI: 5.2; 11.0) at 1600 mg. In an additional study in healthy participants with sparsentan exposure of more than 2 times the maximum recommended dose for humans, no relevant QTcF prolongation occurred; the maximum 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

The efficacy and safety of sparsentan were investigated in PROTECT in patients with IgAN.

PROTECT is a randomised, double-blind (110 weeks), active-controlled, multicentre, global Phase III study in patients with IgAN. The study enrolled patients ≥ 18 years of age, including 15 (8%) sparsentan-treated patients >65 years of age, with an eGFR ≥30 ml/min/1.73 m^2 and a total urinary protein excretion of ≥1.0 g/day. Prior to participation in the study, patients had been taking the maximum tolerated dose of an ACE inhibitor and/or an ARB for at least 3 months. ACE inhibitor and/or ARB treatment was discontinued prior to administration of sparsentan. Patients with baseline potassium levels greater than 5.5 mmol/l were excluded.

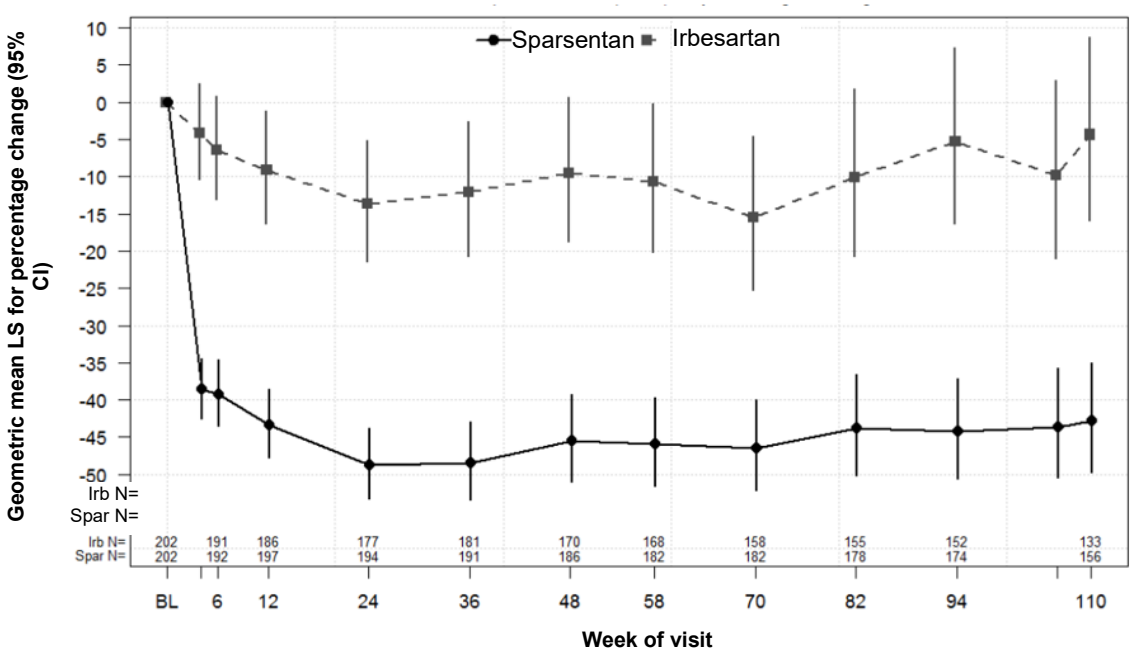
A total of 404 patients were randomised to receive sparsentan (n = 202) or irbesartan (n = 202). Treatment was started with 200 mg sparsentan once daily or 150 mg irbesartan once daily. After 14 days, the dose was titrated to the recommended dose of 400 mg sparsentan once daily or 300 mg irbesartan once daily, depending on tolerability. 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 of 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 study. Other classes of antihypertensives were authorised as needed to achieve the target blood pressure. Treatment with immunosuppressants was permitted during the study at the investigator's discretion.

Baseline data on 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/K) 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 of other ethnicities.

The primary (interim) proteinuria analysis was conducted 36 weeks after randomisation of approximately 280 participants to determine whether the treatment effect of the primary efficacy endpoint, the change in UP/K at week 36 from baseline, was statistically significant. The primary endpoint of the study, the change in the UP/K ratio from baseline at week 36, was met. The geometric mean of the UP/K at week 36 was 0.62 g/g in the sparsentan group compared to 1.07 g/g in the irbesartan group. The geometric mean of the least squares (LS) for the percentage change in UP/K from baseline at week 36 was -49.8% (95% confidence interval [CI]): -54.98, -43.95) in the sparsentan group versus -15.1% (95% CI: -23.72, -5.39) in the irbesartan group (p<0.0001; (Figure 1). In the final analysis, sparsentan showed a rapid and sustained effect of antiproteinuric treatment over a 2-year period with a geometric mean UP/K at week 110 of 0.64 g/g in the sparsentan group versus 1.09 g/g in the irbesartan group, representing a mean reduction of 43% from baseline (95% CI: -49.75, -34.97) compared to only 4.4% with irbesartan treatment (95% CI: -15.84, 8.70). An improvement in proteinuria reduction was observed continuously with sparsentan after only 4 weeks and continued until week 110 (Figure 1).

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



Notes: Adjusted geometric least squares mean for UP/K ratio compared to baseline was based on a longitudinal repeated measures model stratified by eGFR and proteinuria screening and is reported as percentage change along with the respective 95% CI. The analysis includes UP/K data during the double-blind phase from all patients who were randomised and received at least one dose of study drug. Baseline was defined as the last non-missing observation prior to and including the administration of the first dose.

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

Estimated GFR

At the time of confirmatory analysis, the improvement in sustained eGFR reduction at two years (from 6 weeks) 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 overall eGFR reduction (from baseline) was 1.0 ml/min/1.73 m^2 at two years (95% CI: -0.03, 1.94, p = 0.058). The absolute change in eGFR from baseline after 2 years was -5.8 ml/min/1.73 m^2 (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.

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)) investigated the combined use of ACE inhibitors and angiotensin II receptor blockers. The ONTARGET study was conducted in patients with a history of cardiovascular or cerebrovascular disease or type 2 diabetes mellitus with evidence of end-organ damage. VA NEPHRON-D was a study for patients with type 2 diabetes mellitus and diabetic nephropathy. These studies showed no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, with an increased risk of hyperkalaemia, acute kidney injury and/or hypotension observed compared to monotherapy. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers. Therefore, concomitant treatment with ACE inhibitors and angiotensin II receptor blockers should not be used in patients with diabetic nephropathy. The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) study was designed to evaluate the benefit of adding aliskiren to standard therapy with 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 prematurely due to an increased risk of adverse outcomes. Cardiovascular death and stroke occurred more frequently in the aliskiren group than in the placebo group, and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were reported more frequently in the aliskiren group than in the placebo group.

Pharmacokinetics

Absorption

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

After a single oral dose of 400 mg sparsentan, the geometric mean C_{max} is 6.97 µg/ml and the AUC is 83 µg × h/ml. Steady-state plasma levels are reached within 7 days without accumulation of exposure at the recommended dosage.

After a dose of 400 mg sparsentan daily, the geometric mean of the C_{max} at steady state is 6.47 µg/ml and the AUC at steady state is 63.6 µg × h/ml.

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

Distribution

According to a population pharmacokinetic analysis, the apparent volume of distribution at steady state is 61.4 litres.

Sparsentan is highly bound (>99%) to human plasma proteins, preferentially binding to albumin and moderately to acidic alpha-1-glycoprotein.

Metabolism

Sparsentan is mainly metabolised by CYP3A4 with a small ratio of CYP2C8, 2C9 and 3A5. The parent compound is predominant in human plasma and accounts for about 90% of the total radioactivity in the bloodstream. A minor hydroxylated metabolite was the only metabolite in plasma that accounted for >1% of the total radioactivity (about 3%). The major 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. According to a population pharmacokinetic analysis, the apparent clearance is 3.88 l/h and increases to 5.11 l/h at steady state.

The half-life of sparsentan in the steady state is estimated at 9.6 hours.

After a single dose of 400 mg radiolabelled sparsentan, 82% of the dosed radioactivity was recovered within a 10-day collection period: 80% via faeces, of which 9% was in unchanged form, and 2% via urine, of which only a negligible amount was in unchanged form.

Linearity/non-linearity

The C_{max} and AUC of sparsentan increase less than proportionally after 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 after a dose of 400 or 800 mg daily.

Kinetics in specific patient groups

Elderly patients
The population pharmacokinetic analysis showed no significant influence of age on the plasma exposure of sparsentan. No dose adjustment is required in elderly patients (see “Dosage/administration”). Sparsentan has not been studied in patients aged >75 years.

Hepatic impairment
In a relevant study on hepatic impairment, the systemic exposure after a single dose of 400 mg sparsentan in patients with existing (baseline) mild or moderate hepatic impairment (Child-Pugh classification A or Child-Pugh B) was similar to that in 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 “Dosage/Administration” and “Warnings and precautions”).

No data are available on patients with severe hepatic impairment, and therefore, sparsentan is not recommended in these patients (Child-Pugh C classification) (see "Dosage/Administration").

Renal impairment
According to a population pharmacokinetic analysis in patients with chronic kidney disease with mild (creatinine clearance 60-89 ml/min), moderate (creatinine clearance 30-59 ml/min) and severe (creatinine clearance 15-29 ml/min) renal disease, renal impairment has no clinically significant effect on pharmacokinetics compared to normal renal function (creatinine clearance ≥90 ml/min). No data are available for patients with end-stage renal disease (creatinine clearance <15 ml/min).

Due to the limited data available, no dose adjustment can be recommended for patients with severe renal disease (eGFR <30 ml/min/1.73 m^2, see “Dosage/administration”). parsentan has not been studied in dialysis patients or patients with severe renal disease, and therefore, treatment with sparsentan is not recommended in these patients. Sparsentan has not been studied in patients who have received a kidney transplant, therefore sparsentan should be used with caution in this patient population (see “Dosage/Administration”).

Other special populations

Population pharmacokinetic analyses indicate no clinically significant influence of age, gender or ethnicity on the pharmacokinetics of sparsentan.

Preclinical data

In embryofoetal development studies in rats and rabbits, developmental toxicity was observed in both species. In rats, dose-related teratogenic effects in the form of craniofacial malformations, skeletal abnormalities, increased embryofoetal lethality and reduced foetal weight were observed at all doses of sparsentan tested, at exposures 8-fold and 13-fold above the AUC for 800 mg/day and 400 mg/day in humans, respectively. In rabbits, no foetal malformations or effects on embryo or foetal viability or foetal growth occurred, but at exposures of approximately 0.10 and 0.2 times the human AUC at 800 mg/day and 400 mg/day, respectively, there was an increase in skeletal abnormalities (supernumerary rib in the cervical region).

In the pre- and postnatal developmental study in rats, maternal toxicity including death was observed at ~8 and 13 times the human AUC and maternal toxicity was observed at ~2 and 3 times the human AUC at 800 mg/day and 400 mg/day. Increased mortality and decreased growth of young animals occurred at ~8 and 13 times the human AUC, and decreased growth occurred at ~2 and 3 times the human AUC at 800 mg/day and 400 mg/day.

Studies with young animals

Studies in rat pups have shown no general toxicological side effects up to a dose level of 10 mg/kg/day and no reproductive toxicity in males or females up to a dose level of 60 mg/kg/day when dosing was started on postnatal day (PND) 14 (equivalent to one-year-old children). Vascular toxicity occurred at doses ≥3 mg/kg/day when dosing commenced on PND 7 (equivalent to neonates).

Other information

Shelf life

Do not use this medicine after the expiry date which is stated on the pack after "EXP".

Special precautions for storage

Store at 15°C - 30°C.

Keep out of the sight and reach of children.

Instructions for handling

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

Marketing authorisation number

69241 (Swissmedic)

Packs

200 mg/400 mg film-coated tablets: Packs of 30 film-coated tablets in a bottle. (B)

400 mg film-coated tablets: Packs of 30 film-coated tablets in a bottle. (B)

400 mg film-coated tablets: 3 packs of 30 film-coated tablets in a bottle. (B)

Marketing authorisation holder

Vifor (International) Inc, St. Gallen.

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