23 February 2024
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EMADOC-1700519818-1297866
Committee for Orphan Medicinal Products

EMA/COMP position on review of criteria for orphan designation of an orphan medicinal product submitted for marketing authorisation

Filspari (sparsentan)
Treatment of primary IgA nephropathy
EU/3/20/2345

Sponsor: Vifor France

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Sparsentan
Other name(s)	-
International Non-Proprietary Name	Sparsentan
Tradename	Filspari
Orphan condition	Treatment of primary IgA nephropathy
Sponsor's details:	Vifor France Tour Franklin La Defense 8 100 Terrasse Boieldieu 92042 Paris La Defense Cedex France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Retrophin Europe Limited
COMP opinion	18 September 2020
EC decision	19 October 2020
EC registration number	EU/3/20/2345
Post-designation procedural history	
Sponsor's name change Transfer of sponsorship	Name change from Retrophin Europe Limited to Travere Therapeutics Ireland Limited – EC letter of 17 March 2021 Transfer from Travere Therapeutics Ireland Limited to Vifor France – EC decision of 20 December 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Vilma Petrikaite / Patrick Vrijlandt
Applicant	Vifor France
Application submission	20 July 2022
Procedure start	18 August 2022
Procedure number	EMA/H/C/005783
Invented name	Filspari
Proposed therapeutic indication	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). Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Filspari
CHMP opinion	22 February 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Elisabeth Johanne Rook
Sponsor's report submission	21 September 2022
COMP discussion	7-9 November 2023
COMP opinion (adoption via written procedure)	23 February 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2020 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing sparsentan was considered justified based on non-clinical in vivo data showing a normalisation of creatinaemia and proteinuria;
- the condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney failure requiring dialysis and transplantation;
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition/for the population at risk of developing the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing sparsentan as an orphan medicinal product for the orphan condition: treatment of primary IgA nephropathy".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Primary Immunoglobulin A nephropathy (IgAN) is a chronic kidney disease (CKD) frequently leading to end stage renal disease (ESRD). IgAN is the most common primary glomerulonephritis in the world and the prevalence rate varies across different geographical regions.

Primary IgAN is a form of glomerular disease that is diagnosed from a kidney biopsy and is characterized by the finding of immune deposits, predominantly containing polymeric immunoglobulin A (IgA), in the glomerular mesangium of the kidney (Berger 1968; Barratt 2011; Boyd 2012; Le 2012). These immune deposits cause a cascade of events that include proliferation of the mesangial

cells, synthesis of extracellular matrix, and excess production of inflammatory cytokines, resulting in damage to the glomerular filtration barrier, proteinuria, hematuria, and decreased glomerular filtration rate.

The approved therapeutic indication "*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)"* falls within the scope of the designated orphan condition "Treatment of primary IgA nephropathy".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

IgAN is a progressive disease in which 20–40% of patients progress to end stage renal disease within 10–20 years of diagnosis (Manno et al., 2007; Berthoux et al., 2011; Moriyama et al., 2014). In a minority of cases, patients may develop nephrotic syndrome (Pattrapornpisut et al., Am J Kidney Dis. 78(3):429-441). Many patients are diagnosed in their 20s or 30s and therefore, face the prospect of dialysis or the need for kidney transplantation in the prime of their lives. It is estimated that IgAN accounts for 10% of renal transplants among patients with primary glomerulonephritis in the US, and between 7 – 20% of patients in Europe and Australia in long-term dialysis and renal transplantation programs. Post-transplant recurrence of IgAN is common (Moroni et al., 2013).

The COMP considers this condition as life-threatening and chronically debilitating due to progressive loss of kidney function leading to end-stage renal disease requiring dialysis and transplantation.

Number of people affected or at risk

An average prevalence of 4.6 in 10,000 was proposed for the overall population in Europe. The sponsor has based the prevalence on the individual incidences reported for each member state in the 41 articles they selected for the prevalence calculation. These were then multiplied by the expected life-expectancy from the age of diagnosis.

From these publications they made the following assumptions. **Average age at diagnosis of Primary IgAN:** The average age at diagnosis has been reported for a number of Member States. In cases where average age at diagnosis was not available, the average age of 36 years as reported in the European Validation Study of the Oxford Classification of IgAN (VALIGA) study was imputed as value. This study included 1147 patients from 13 European countries (Croatia, Czech Republic, Estonia, Germany, Greece, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Turkey, UK) with biopsy-proven primary IgAN and adequate histology material available for review (Coppo 2014). Average ages at the time of diagnosis for each EEA-country are presented in Table 1.

Table 1. Average age at IgAN diagnosis

Country	Reference	Title	Age at diagnosis	Average age at diagnosis*
Austria	--			*36*
Belgium	--			*36*
Bulgaria	--			*36*
Croatia	--			*36*
Cyprus	--			36
Czech Republic	Maixnerova 2015	Nationwide biopsy survey of renal diseases in the Czech Republic during the years 1994-2011	33	33
	Maixnerova 2012	The retrospective analysis of 343 Czech patients with IgA nephropathy-one centre experience	32	
	Rychlík 2004	The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994-2000	30	
Denmark	--		--	*36*
Estonia	Riispere 2012	Occurrence of kidney diseases and patterns of glomerular disease based on a 10-year kidney biopsy material: A retrospective single-centre analysis in Estonia	35	35
Finland	Geddes 2003	A tricontinental view of IgA nephropathy	35	35
France	Berthoux 2011	Predicting the Risk for Dialysis or Death in IgA Nephropathy	41	39
	Moranne 2008	Primary glomerulonephritis: an update on renal survival and determinants of progression	37	
	Simon 1994	Epidemiology of primary glomerular diseases in a French region. Variations according to period and age	38	
	Frimat 1994	Annual incidence of IgA nephropathy (Berger disease) and Henoch-Schönlein purpura in eastern France	38	
	Asgarali 2021	Increased incidence and improved prognosis of glomerulonephritis: a national 30-year study	47	

Country	Reference	Title	Age at diagnosis	Average age at diagnosis*
Germany	--		--	*36*
Greece	--		--	*36*
Hungary	--		--	*36*
Ireland	--		--	*36*
Italy	Manno 2007	A novel simpler histological classification for renal survival in IgA nephropathy: A retrospective study	31	31
Latvia	--		--	*36*
Lithuania	--		--	*36*
Luxembourg	--		--	*36*
Malta	--		--	*36*
Netherlands	--		--	*36*
Poland	Perkowska-Ptasinska 2016	Kidney disease in the elderly: biopsy-based data from 14 renal centres in Poland	37 (18-64 yrs)	37
Portugal	--		--	*36*
Romania	--		--	*36*
Slovakia	--		--	*36*
Slovenia	--		--	*36*
Spain	--		--	*36*
Sweden	Jarrick 2017	Clinical validation of immunoglobulin A nephropathy diagnosis in Swedish biopsy registers	39	41
	Peters 2015	Increased risk of renal biopsy complications in patients. with IgA-nephritis	42	
Iceland	--		--	*36*
Liechtenstein	--		--	*36*
Norway	Knoop 2015	Addition of eGFR and Age Improves the Prognostic Absolute Renal Risk-Model in 1,134 Norwegian Patients with IgA Nephropathy	38	39
	Knoop 2013	Mortality in patients with IgA nephropathy	39	

Country	Reference	Title	Age at diagnosis	Average age at diagnosis*
	Bjorneklett 2012	Long-term risk of EKRD in IgAN; validation of Japanese prognostic model in a Norwegian cohort	39	

* The mean age of 36 years (in italic) from the VALIGA study has been used for estimating mean age when country-specific numbers are not available.
eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; IgA=immunoglobulin A; IgAN=immunoglobulin A nephropathy

Life expectancy in patients diagnosed with IgAN: IgAN patients have been shown to have higher mortality than the general population. Two key references are used as basis for estimation of life expectancy in IgAN patients: Knoop (2013) and Jarrick (2019).

Knoop (2013) report a Standardized Mortality Ratio (SMR) of 1.9 (95% CI, 1.5-2.4) based on a cohort study of 633 IgAN patients in Norway, relating it to the Norwegian total population to obtain an estimate of the SMR.

Skriver (2018) provide a formula for the relationship between loss of life expectancy and SMR that works reasonably well for computations at age 30:

Change in life expectancy = $-K \times \ln(SMR)$ where K=10 for men and K=9 for women in the Nordic countries. Because the mean age at diagnosis is 36 years for IgAN, this model for transformation of SMR to change in life expectancy is judged to be appropriate for the current derivation of life expectance at diagnosis (ie, duration of disease). Assuming approximately 70% of IgAN patients are male, and 30% female we use K=9.7, which is a weighted average for males and females. Based on the formula by Skriver (2018), an SMR of 1.9, reported by Knoop (2013), corresponds to a reduction of life expectancy of 6.2 years for IgAN patients compared to the healthy population.

Jarrick (2019) report estimates of survival in a cohort of 3622 IgAN patients in Sweden and a matched control group of 18041 persons. Median age at death was 77.0 years (95% CI, 75.9 to 78.0) in patients with IgAN, compared with 83.0 years (95% CI, 82.4 to 83.5) in controls, representing a reduction in median life expectancy of 6.0 years. The estimated reduction in life expectancy of 6.0 years is strikingly close to the estimate derived from the SMR reported by Knoop (2013).

Disease duration is calculated as latest available life expectancy data (ie, life expectancy in 2019) in the general population at the mean age of diagnosis minus the estimated reduction in mean life expectancy due to IgAN diagnosis.

The sponsor concludes that patients have a life-expectancy of 40 years which they state is a median of 77 years and thus less than the current average which is 83 years.

Estimation of prevalence (P)

In Table 2, the country-specific estimates of prevalence are based on statistics on population size as of 1 Jan 2021 by country obtained from Eurostat on 28 October 2021 together with the incidence reported in the literature and estimation of life expectancies in patients diagnosed with IgAN.

Table 2: Prevalence by country and in the EEA in total

Country	Population as of 1 Jan 2021	Incidence (pmp)	Neighbouring countries for extrapolation of incidence	Life expectancy IgAN (Knoop 2013)	Prevalence (per 10,000) (Knoop 2013)	Affected population (Knoop 2013)	Life expectancy IgAN (Jarrick 2018)	Prevalence (per 10,000) (Jarrick 2018)	Affected population (Jarrick 2018)
Austria	8,932,664	13.2	Germany	40.6	5.4	4,785	40.8	5.4	4,808
Belgium	11,566,041	22.3		40.7	9.1	10,498	40.9	9.1	10,550
Bulgaria	6,916,548	8.3	Croatia, Hungary	34.3	2.8	1,958	34.5	2.8	1,970
Croatia	4,036,355	9.6		37.3	3.6	1,447	37.5	3.6	1,455
Cyprus	896,005	6.3		40.9	2.6	231	41.1	2.6	233
Czech Republic	10,701,777	11.6		37.1	4.3	4,606	37.3	4.3	4,631
Denmark	5,840,045	1.8		40.0	0.7	421	40.2	0.7	423
Estonia	1,330,068	14.0		38.7	5.4	721	38.9	5.4	725
Finland	5,533,793	21.5		41.8	9.0	4,972	42.0	9.0	4,996
France	67,439,599	15.8		38.9	6.1	41,386	39.1	6.2	41,599
Germany	83,155,031	13.2		39.9	5.3	43,769	40.1	5.3	43,988
Greece	10,682,547	8.4	Macedonia, Serbia	40.4	3.4	3,624	40.6	3.4	3,642
Hungary	9,730,772	5.6		35.2	2.0	1,904	35.4	2.0	1,915
Iceland	368,792	10.1	Norway	41.6	4.2	155	41.8	4.2	156
Ireland	5,006,907	11.5	UK	41.3	4.8	2,383	41.5	4.8	2,395
Italy	59,257,566	12.5		47.0	5.9	34,739	47.2	5.9	34,887
Latvia	1,893,223	11.7	Lithuania	34.9	4.1	774	35.1	4.1	778
Liechtenstein	39,055	4.1	Switzerland	42.3	1.7	7	42.5	1.7	7
Lithuania	2,795,680	11.7		35.7	4.2	1,168	35.9	4.2	1,175
Luxembourg	634,730	14.4	France (Metropolitan), Germany	41.3	6.0	378	41.5	6.0	380
Malta	516,100	12.5	Italy	41.8	5.2	270	42.0	5.2	271
Netherlands	17,475,415	16.3		40.8	6.7	11,646	41.0	6.7	11,703
Norway	5,391,369	10.1		38.7	3.9	2,104	38.9	3.9	2,115
Poland	37,840,001	1.1		36.0	0.4	1,499	36.2	0.4	1,507

Portugal	10,298,252	6.5		40.5	2.6	2,712	40.7	2.6	2,725
Romania	19,186,201	10.0		34.7	3.5	6,658	34.9	3.5	6,696
Slovakia	5,459,781	11.6	Czech Republic	36.8	4.3	2,331	37.0	4.3	2,344
Slovenia	2,108,977	9.6	Croatia	40.1	3.9	813	40.3	3.9	817
Spain	47,394,223	7.9		42.4	3.3	15,876	42.6	3.4	15,951
Sweden	10,379,295	11.7		36.9	4.3	4,465	37.1	4.3	4,489
EEA Total	**452,806,812**	**11.2**		**40.1**	**4.6**	**208,141**	**40.3**	**4.62**	**209,171**

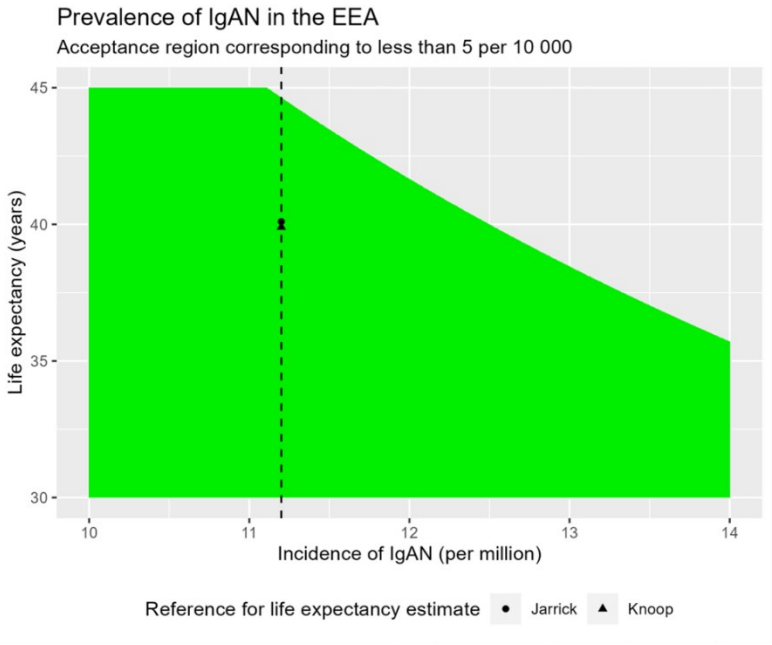
EEA=European Economic Area; IgAN=immunogloblin A nephropathy; pmp=per million population

Sensitivity analyses were performed to assess the sensitivity of the conclusion that the prevalence is less than the upper level of acceptance of 5 per 10 000. An overall picture of which combinations of incidence and life expectancy at diagnosis that correspond to a prevalence of less than 5 per 10 000 people is shown as a green coloured area in Figure 2.

The prevalence of primary IgAN is calculated from an estimated incidence of 11.2 obtained from a systematic literature review and the estimated mean duration of disease estimated from survival data in 2 IgAN cohorts reported by Knoop (2013) and Jarrick (2018), 40.1 and 40.3 years, respectively. These 2 estimates are included in figure 1 as a triangle and as a circle, respectively. These estimates of life expectancy at diagnosis correspond to a mean reduction of life expectancy of approximately 6 years compared to a healthy population. Hence the upper limit of the plot of 45 years life expectancy at diagnosis correspond to a reduction of life expectancy of approximately 1 year only, which is judged to be very unlikely. Given that the 2 separate and independent estimates are very close to each other, the potential deviation with respect to the assumed life expectancy from diagnosis is believed to be considerably smaller. Given the assumed life expectancy at diagnosis of approximately 40 years, any incidence of no more than 12.5 per million person years correspond to a prevalence less than 5 per 10,000 (Figure 1).

In conclusion, it is judged that the prevalence estimate of 4.5 in 10 000 people is robust and meet the criteria of less than 5 in 10 000 people, which is the threshold for being a rare disease in the EEA.

Figure 1. Sensitivity analysis showing combinations of incidence rate and life expectancy at diagnosis providing a prevalence estimate of 5 in 10 000 or less



Dotted line indicates the weighted incidence of 11.2 pmp in the EEA
EEA=European Economic Area; IgAN=immunogloblin A nephropathy; pmp=per million population

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There is one product which is authorised for use in the condition namely Kinpeygo. Its current indication is: "*Kinpeygo is indicated for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN) in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram*".

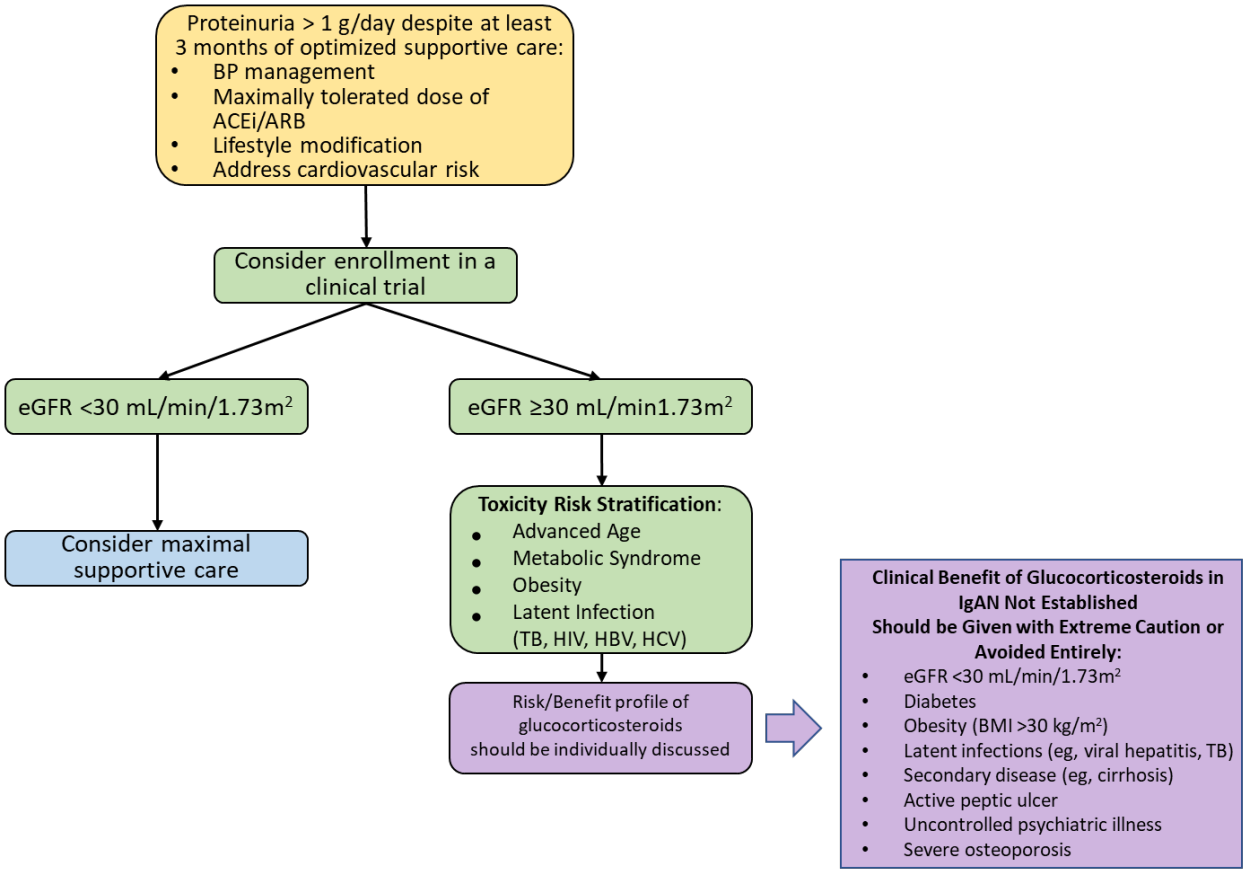
Treatment recommendations are outlined in the KDIGO 2021 guideline. Standard of care comprises supportive therapy, which focuses on a lowering of proteinuria and optimal blood pressure control by maximum tolerated inhibition of the Renin-angiotensin system (RAS), together with a low sodium Orphan Maintenance Assessment Report EMA/OD/0000066260 Page 6/7 diet (KDIGO 2021, Trimarchi et al 2019). For patients with persistent proteinuria >1 g/day, rigorous blood pressure control with ACEIs (Angiotensin-converting enzyme (ACE) inhibitors) and/or ARBs [Angiotensin II receptor blocker] to achieve blood pressure targets of <130/80 mmHg is the cornerstone of therapy. When proteinuria persists despite optimal RAS inhibition with ACEs/ARBs patients are at risk of progression to ESRD, there are no further recommended treatments, and management options are generally limited to consideration of an off-label 6-month treatment course of high-dose systemic glucocorticosteroids (other than Kinpeygo).

Of note, the COMP has previously considered Sandimmun as a satisfactory method for the treatment of primary IgA nephropathy in initial orphan designations. Sandimmun is an oil-based formulation of

ciclosporin and has been authorised through a referral procedure across the EU for the treatment of nephrotic syndrome in diverse renal conditions covering IgAN (i.e. steroid dependent and steroid resistant nephrotic syndrome due to primary glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis) https://www.ema.europa.eu/en/documents/referral/sandimmun-article-30-referral-annex-iii_en.pdf

The currently accepted treatment paradigm for primary IgAN, which also represents standard of care in Europe, entails optimized supportive care including maximal renin-angiotensin-aldosterone system (RAAS) blockade therapy (maximum labelled or tolerated dose of an ACEI or ARB), to control blood pressure and reduce proteinuria (Locatelli 2006; Aucella 2009; Floege 2011; KDIGO 2021). However, it should be noted that neither ACEIs nor ARBs are formally approved for the treatment of IgAN. Those patients with proteinuria >1 g/day despite optimised supportive care remain at risk of disease progression and renal failure. The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends enrolling these patients in clinical trials before considering treatment with glucocorticosteroids because of the poorly defined benefit-risk assessment for glucocorticosteroids in IgAN due to a paucity of randomised controlled studies to demonstrate benefit and of the known safety and tolerability profile of glucocorticosteroids (KDIGO 2012; KDIGO 2021; Figure 2).

Figure 2. Management of patients with IgAN who remain at high risk of progression after maximal supportive care



Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgAN = immunoglobulin A nephropathy; TB = tuberculosis.
Source: Adapted from KDIGO 2021.

The COMP noted that the exact therapeutic indication wording and target population for Filspari as per 4.1 of the SmPC, *does not fully overlap* with the therapeutic indication of Sandimmun, as Filspari is also indicated for in patients with proteinuria who do not formally meet the criterion of nephrotic syndrome. Sandimmun is therefore not considered a satisfactory method in this case.

It was also noted that the exact therapeutic indication wording and target population for Filspari as per 4.1 of the SmPC is broader than that for Kinpeygo and thus there is no full overlap with the therapeutic indication of Kinpeygo. Kinpeygo is not considered a satisfactory method for the entirety of the target patients population that is covered by the therapeutic indication of Filspari, i.e. patients with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g) whilst Kinpeygo is indicated for adult IgAN patients at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram.

Significant benefit

Not applicable.

4. COMP list of issues

No applicable.

5. COMP position adopted on 23 February 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of primary IgA nephropathy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney failure requiring dialysis and transplantation;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Filspari.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Filspari, sparsentan for treatment of primary IgA nephropathy (EU/3/20/2345) is not removed from the Community Register of Orphan Medicinal Products.