31 May 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Kinpeygo (budesonide)
Treatment of primary IgA nephropathy
EU/3/16/1778

Sponsor: STADA Arzneimittel AG

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	Budesonide
Other name(s)	--
International Non-Proprietary Name	Budesonide
Tradename	Kinpeygo
Orphan condition	Treatment of primary IgA nephropathy
Sponsor's details:	STADA Arzneimittel AG Stadastrasse 2-18 Dortelweil 61118 Bad Vilbel Hesse Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharmalink AB
COMP opinion	6 October 2016
EC decision	18 November 2016
EC registration number	EU/3/16/1778
Post-designation procedural history	
Sponsor's name change	Name change from Pharmalink AB to Calliditas Therapeutics AB – EC letter of 23 January 2018
COMP opinion on review of orphan designation at the time of marketing authorisation	20 May 2022
Transfer of sponsorship	Transfer from Calliditas Therapeutics AB, Sweden, to STADA Arzneimittel AG, Germany – EC decision of 13 September 2022
Type II variation procedural history	
Rapporteur / Co-rapporteur	Christian Gartner / Martina Weise
Applicant	STADA Arzneimittel AG
Application submission	28 September 2023
Procedure start	28 October 2023
Procedure number	EMA/H/C/005653/II/0008
Invented name	Kinpeygo
Proposed therapeutic indication	Kinpeygo 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 ≥0.8 g/g)" Further information on Kinpeygo can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/kinpeygo
CHMP opinion	30 May 2024

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Armando Magrelli
Sponsor's report submission	9 November 2023, 11 March 2024, 16 April 2024 and 29 April 2024
COMP discussion	21-23 May 2024
COMP opinion (adoption via written procedure)	31 May 2024

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 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 budesonide was considered justified based on clinical data showing improvement of kidney function in patients treated with the proposed product;
- 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 that has been authorised in the European Union for patients affected by 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 budesonide as an orphan medicinal product for the orphan indication: treatment of primary IgA nephropathy.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2022 was based on the following grounds:

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 approximately 4 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 which could ultimately lead to end-stage renal disease 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 Kinpeygo.

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 Kinpeygo, budesonide for treatment of primary IgA nephropathy (EU/3/16/1778) is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of type II variation

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 IgA nephropathy (IgAN) is an auto-immune disorder with nephropathy, caused by deposit of autoimmune-complexes, such as galactose-deficient IgA1 antibodies (Gd-IgA1), in the glomeruli of the kidney. In the majority of patients, there is a progressive loss of kidney function. This leads to end-stage renal disease requiring dialysis and transplantation in about 20–40% of patients within 10–20 years of diagnosis.

Kinpeygo is currently 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*".

This type II variation implies a broadening of the target population, no longer restricted for use in patients with rapid disease progression and with very severe proteinuria.

With this type II variation, the therapeutic indication is changed into: "*Kinpeygo 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 ≥0.8 g/g)"*, which still 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

Although in some patients the disease is self-limiting, the majority of patients suffer from a progressive loss of kidney function, which leads to end-stage renal disease requiring dialysis and transplantation in about 20–40% of the cases within 10–20 years after diagnosis (Manno et al., 2007; Berthoux et al., 2008; Moriyama et al., 2014). Most patients are diagnosed in their 20s or 30s. Recurrence of IgAN in the donor kidney after transplantation is common (Choy et al., 2006). Current treatment options are not ultimately curative.

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

Number of people affected or at risk

The COMP established the prevalence as approximately 4/10,000 during the initial orphan maintenance procedure back in 2022.

The sponsor has performed a literature search in PubMed to evaluate whether there were any new relevant publications available since 2022, that could inform the prevalence estimate in the EU. One publication was found (Willey et al. Nephrol Dial Transplant. 2023 Oct; 38(10): 2340–2349.) , which is a systematic literature review of studies on the incidence and prevalence of biopsy-confirmed IgAN, based on national kidney biopsy registry data in European countries, published between 1990 to 2020. IgAN point prevalence was estimated by the authors as the annual IgAN incidence multiplied by the estimated duration of disease (defined as time to kidney replacement therapy, KRT). Across 10 European countries, the pooled IgAN point prevalence was 2.53 per 10,000. When including regional studies of 4 additional countries, the pooled IgAN point prevalence increased to 3.58 per 10,000.

These estimates by Willey et al are lower than previous established in orphan designation for IgAN. This difference may be due as disease duration was defined differently in the Wiley study (as time to kidney replacement), which may not represent the full disease duration (defined as overall survival after the diagnosis) for the majority of patients who will never reach the point that they need or actually receive a kidney transplantation, or dialysis. Thus, this might have led to an underestimation of the indirect calculated prevalence. Moreover, there are considerable regional differences in Europe, with higher incidences in northern regions. A different selection of sources in the Willey study, might also have led to a different estimate than established for this condition before. There are no indications from the literature that there is a decreasing trend in the incidence of IgAN in Europe.

Considering the above, the COMP decided to keep the originally adopted prevalence estimate of approximately 4 in 10,000 persons.

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

Currently there are two products authorized in the EU for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN), these are Kinpeygo itself as well as Filspari. In addition, Sandimmun is authorized in the EU for a partially overlapping patient population in relation to the one of Kinpeygo.

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) with angiotensin converting enzyme (ACE) inhibitors or angiotensin AT(1)-receptor blockers (ARBs), together with a low sodium diet (KDIGO 2021, Trimarchi et al 2019). However, it should be noted that neither ACEIs nor ARBs products are currently authorised for the treatment of IgAN, and therefore these are not considered formally as satisfactory methods.

On 19th April 2024, the European Commission adopted a decision of conditional marketing authorisation (CMA) for Filspari (sparsentan), 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).* Sparsentan is a novel dual endothelin angiotensin receptor antagonist, belonging to the class of renin-angiotensin system (RAS) inhibitors. While the indication of Filspari is completely overlapping with the revised indication for Kinpeygo, it is not considered to be a satisfactory method for the purpose of the maintenance of the orphan designation of Kinpeygo for the following reason:

At time of the COMP discussion on the orphan maintenance of Kinpeygo on 21 May 2024, the notification of marketing authorisation for Filspari had not yet been published in the Official Journal of the European Union. Therefore, Filspari was not considered a satisfactory method in this orphan maintenance procedure of 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 an article 30 referral procedure in the EU for the treatment of nephrotic syndrome in diverse renal conditions covering IgAN as well (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 COMP noted that the exact therapeutic indication wording and target population for Kinpeygo as per 4.1 of the SmPC, does not fully overlap with the therapeutic indication of Sandimmun, as Kinpeygo 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 orphan maintenance procedure of Kinpeygo.

Significant benefit

Not applicable.

4. COMP position adopted on 31 May 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 approximately 4 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 Kinpeygo.

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 Kinpeygo, budesonide, for treatment of primary IgA nephropathy (EU/3/16/1778) is not removed from the Community Register of Orphan Medicinal Products.