15 July 2022
EMA/OD/0000066260
EMADOC-360526170-1063106
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Kinpeygo (budesonide)
Treatment of primary IgA nephropathy
EU/3/16/1778
Sponsor: Calliditas Therapeutics AB

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information 3

2. Grounds for the COMP opinion 4

2.1. Orphan medicinal product designation 4

3. Review of criteria for orphan designation at the time of marketing authorisation 4

Article 3(1)(a) of Regulation (EC) No 141/2000 4

Article 3(1)(b) of Regulation (EC) No 141/2000 5

4. COMP position adopted on 20 May 2022 7

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:	Calliditas Therapeutics AB Kungsbron 1 111 22 Stockholm Stockholms Lan Sweden
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
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Andrea Laslop / Martina Weise
Applicant	Calliditas Therapeutics AB
Application submission	28 May 2021
Procedure start	17 June 2021
Procedure number	EMA/H/C/005653
Invented name	Kinpeygo
Therapeutic indication	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. 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	19 May 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Elisabeth Johanne Rook
Sponsor's report submission	7 July 2021
COMP discussion	10-12 May 2022
COMP opinion (adoption via written procedure)	20 May 2022

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 in 2016 designation was based on the following grounds:

- 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;
- 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.

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

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.

The pathogenesis of primary IgA nephropathy is related to aberrantly glycosylated, galactose-deficient IgA1 that originate from the Peyer patches in the gastrointestinal mucosa. As such the pathogenesis is different from that of secondary forms of IgA nephropathy where the origin of IgA is heterogeneous (e.g. in the context of an autoimmune response), and primary IgA nephropathy is considered to be primarily a disease of the mucosal system. Related to this, the proposed product is expected to act locally on the Peyer patches in the intestinal mucosa, with low systemic absorption, addressing specifically the pathophysiology of primary but not secondary forms of IgA nephropathy. Thus, the COMP has previously decided that primary IgA nephropathy can be considered a medical entity valid for designation.

The approved therapeutic indication "*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."* 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.

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., 2008; Moriyama et al., 2014). Most 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. When compared to a group of non-diabetic patients who had received kidney transplants, kidney transplant patients with a primary diagnosis of IgAN had a higher cumulative graft failure rate, with the diagnosis of IgAN identified as an independent predictor of worse outcome in the long-term (Moroni et al., 2013). For IgAN patients with prior graft loss due to recurrent IgAN, the risk of IgAN recurrence in the second transplanted kidney (20–100%) is greatly increased (Choy et al., 2006). None of the current available immunosuppressive medicinal products are able to prevent the histological recurrence of IgAN (Floege, 2004).

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

The sponsor proposed a prevalence estimate of 4 in 10.000. This value is in line with the previously accepted estimate from the initial orphan designation in 2016.

At the time of the original application in June 2016, and due to changes in case definition of IgA nephropathy and lack of standardized diagnosis across Europe and across the time span examined (from 1996 to 2016), the sponsor presented their own survey across European centres collecting information, Based on this, the EU prevalence of primary IgAN was set to approximately 4 in 10,000.

For this maintenance report the sponsor has performed a new systematic search of peer-reviewed published medical literature on PubMed up to the current date (i.e. 24 June, 2021). No new information was found that would alter the conclusion on prevalence from the positive opinion by COMP in 2016 of approximately **4 in 10,000**.

The COMP agreed with the proposed prevalence estimate by the sponsor.

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 are currently no treatments approved for the management of patients with primary IgAN. 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

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 [RAS inhibitor therapy] to achieve blood pressure targets of <130/80 mm Hg is the cornerstone of therapy. When proteinuria persists despite optimal RAS inhibition with ACEIs/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 (GCS).

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

However, considering that the exact therapeutic indication wording and target population for Kinpeygo as per 4.1 of the SmPC, is now known and there is no full overlap with the therapeutic indication of Sandimmun, as Kinpeygo is also indicated for in patients with proteinurea who do not formally meet the criterion of nephrotic syndrome, it is not considered that Sandimmun is a satisfactory method in this case.

Significant benefit

Not applicable.

4. COMP position adopted on 20 May 2022

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.