28 February 2025
EMA/OD/0000224423
EMADOC-1700519818-1953155
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Fabhalta (iptacopan)
Treatment of C3 glomerulopathy
EU/3/18/2104

Sponsor: Novartis Europharm Limited

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1. Product and administrative information

Product	
Designated active substance(s)	(4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1))
Other name(s)	--
International Non-Proprietary Name	Iptacopan
Tradename	Fabhalta
Orphan condition	Treatment of C3 glomerulopathy
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion	8 November 2018
EC decision	14 December 2018
EC registration number	EU/3/18/2104
Type II variation procedural history	
Rapporteur	Janet Koenig
Applicant	Novartis Europharm Limited
Application submission	2 July 2024
Procedure start	20 July 2024
Procedure number	EMEA/H/C/005764/II/0001
Invented name	Fabhalta
Therapeutic indication	Treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated. Further information on Fabhalta can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/fabhalta
CHMP opinion	27 February 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Vallo Tillmann
Sponsor's report submission	31 July 2024
COMP discussion and adoption of list of questions	21-23 January 2025
COMP opinion (adoption via written procedure)	28 February 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2018 designation 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 (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) was considered justified based on non-clinical in vivo data showing an improvement in reduction of proteinuria and kidney damage;
- the condition is life-threatening and chronically debilitating due to the development of nephrotic syndrome and end-stage kidney disease leading to renal failure;
- the condition was estimated to be affecting approximately 1.2 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.

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 (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) as an orphan medicinal product for the orphan indication: treatment of C3 glomerulopathy.

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

Complement 3 glomerulopathy (C3G) is rare, complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury caused by dysregulation of the alternative pathway (AP) of the innate complement system, leading to excessive C3 (Complement 3) fragment deposition within the glomerular microenvironment. The ensuing immune-mediated injury manifests as proliferative glomerulonephritis and capillary-wall remodelling, contributing to significant renal pathology.

Approximately 25% of C3G patients exhibit genetic variants or genomic rearrangements in complement genes, while more than half harbour anti-complement autoantibodies, most commonly C3 nephritic factors (Servais et al., 2012; Smith et al., 2019; Noris et al., 2023).

C3G is diagnosed through renal biopsy, characterized by dominant C3 deposition in the glomerulus, as identified by immunofluorescence microscopy. The nomenclature was established by a panel of experts in a 2013 consensus report (Pickering et al., 2013), though the disease itself has been recognized in various forms for decades. The improved understanding of complement-mediated kidney diseases has led to the classification of C3G as a distinct entity within the membranoproliferative glomerulonephritis (MPGN) spectrum. MPGN represents a rare histologic pattern of glomerular injury, defined by hypercellularity, endocapillary proliferation, and capillary wall thickening with characteristic double contours on light microscopy. A definitive diagnosis of C3G is made when C3 deposition is at least two orders of magnitude greater than any immunoglobulin deposition, differentiating it from immune complex-mediated MPGN (IC-MPGN), which exhibits prominent immunoglobulin deposits (Sethi et al., 2011; Cook and Pickering, 2015; Wong et al., 2021). Furthermore, electron microscopy findings allow subclassification of C3G into C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) (Bomback et al., 2018).

Epidemiologically, C3G demonstrates a male predominance, with a male-to-female ratio of approximately 2:1 (Lee et al., 2013; Bomback et al., 2018; Zahir et al., 2021). This condition predominantly affects individuals under 40 years of age, with 30-40% of cases diagnosed in patients younger than 18 years (Smith et al., 2019). The clinical presentation of C3G is highly variable, ranging from asymptomatic urinary abnormalities with preserved renal function to progressive chronic kidney disease (CKD) or rapidly progressive glomerulonephritis (RPGN) (Riedl et al., 2017; Caravaca-Fontán et al., 2020a; Khandelwal et al., 2021; Sheng et al., 2023). Approximately 10% of patients present with proteinuria, while 30% maintain a normal estimated glomerular filtration rate (eGFR) (Caravaca-Fontán et al., 2022b). However, more commonly, patients experience haematuria, sub-nephrotic or nephrotic-range proteinuria, hypertension, peripheral edema, appetite loss, sleep disturbances, and fatigue (Tyagi et al., 2019; Proudfoot et al., 2023a).

C3G is associated with a poor prognosis, with approximately 50% of adult patients progressing to end-stage renal disease (ESRD)within 10 years of diagnosis (Smith et al., 2019). Although kidney transplantation serves as a potential treatment for ESRD, persistent AP dysregulation leads to disease recurrence in 50-84% of the donor recipients. The similarity in disease mechanisms, histological changes, and complement biomarker profiles between native and recurrent C3G highlights the ongoing challenge in managing this condition (Zand et al., 2014; Salvadori and Bertoni, 2016; Wong et al., 2023).

The approved therapeutic indication "*FABHALTA is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated (see section 5.1)*" falls within the scope of the designated orphan condition "treatment of C3 glomerulopathy".

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

C3 glomerulopathy (C3G) is a severe and chronic kidney disease (CKD) characterized by poor prognosis and significant morbidity.

The clinical presentation of C3G is highly variable, ranging from asymptomatic findings to severe progressive CKD or rapid progressive glomerulonephritis (RPGN) (Riedl et al., 2017; Caravaca-Fontán et al., 2020a; Khandelwal et al., 2021; Sheng et al., 2023).

Only 10% of patients present with proteinuria <1 g/day (representing mild disease), and 30% have a normal estimated glomerular filtration rate (eGFR) at diagnosis (Caravaca-Fontán et al., 2022b). Most patients, however, exhibit haematuria, sub-nephrotic or nephrotic range proteinuria, arterial hypertension, peripheral edema, fatigue, and other debilitating symptoms (Tyagi et al., 2019; Proudfoot et al., 2023a). Nephrotic-range proteinuria, common in these patients, is associated with severe acute complications including infection, thrombosis, thromboembolism, and dyslipidaemia, all of which worsen outcomes (Ravindran et al., 2018; Lomax-Browne et al., 2022). These physical effects are compounded by psychological impacts such as anxiety, depression, and frustration, which disrupt patients' social, educational, and vocational development (Lafayette et al., 2024).

A significant proportion of adult patients—up to 50%—progress to ESRD within a decade of diagnosis (Smith et al., 2019). Kidney transplantation is a potential treatment option when kidney failure develops. However, disease recurrence post-transplantation occurs in 50-84% of recipients, with a median recurrence time of 14-28 months (Zand et al., 2014; Regunathan-Shenk et al., 2018; Caravaca-Fontán et al., 2023a). Graft loss is common, affecting more than 50% of recipients within 4-6 years, primarily due to recurrent C3G (Zand et al., 2014; Regunathan-Shenk et al., 2018; Caravaca-Fontán et al., 2023a; Patry et al., submitted; Martinatto et al., 2024). The disease mechanism, clinical course, and risk of kidney failure are similar in native and recurrent C3G (Salvadori & Bertoni, 2016; Wong et al., 2023).

The COMP is of the opinion that the condition remains life-threatening and chronically debilitating.

Number of people affected or at risk

At the time of the initial orphan designation in 2018, the prevalence of C3G in the European Union (EU) was estimated at less than 1.2 per 10,000 population. Updated analyses now suggest a prevalence range of 0.41–0.97 per 10,000, which according to the sponsor, reflects improved methodologies and more specific data on C3G.

Initially, the prevalence estimate relied solely on the median renal survival duration from Servais et al. (2012). The updated estimate, however, incorporates additional data on expected life expectancy after kidney transplantation from the ERA Registry Annual Report (2021), accounting for the recurrence of C3G post-transplantation. This led to an estimated disease duration of 28.5–41.2 years, compared to the 23 years used in the earlier calculation.

Notably, in 2018, prevalence was inferred using data for membranoproliferative glomerulonephritis (MPGN), a broader disease category under which C3G was classified. Since then, C3G has been recognized as a distinct condition, enabling prevalence calculations based solely on C3G-specific epidemiological data. Observational studies by Caravaca-Fontán et al. (2023b) and Medjeral-Thomas et al. (2014) reported annual C3G incidence rates of less than 1–2 per million population in Europe. Using this incidence data and the updated disease duration, the sponsor calculated a C3G prevalence of 0.41–0.97 per 10,000 population.

In the literature, transition from C3G to IC-MPGN (immune-complex-MPGN) and vice versa in serial biopsies has been described (Hou H et al. Kidney International 2014;85:450-456), and misspecification of the diagnosis is not fully excluded. However, the current division of patients into IC-MPGN and C3G diagnostic groups did not reveal substantial differences in the overall or renal survival after diagnosis in a Finnish study (Cells 2023, 12, 712. https://doi.org/10.3390/ cells12050712).

The sponsor adopted conservative assumptions throughout the process. For example, it was assumed that all C3G patients received kidney transplants and experienced disease recurrence, despite high variability in transplantation practices and the faster graft loss associated with C3G recurrence (Martinatto et al. 2024; Zand et al. 2014). This might explain that the U.S. National Organization for Rare Disorders (NORD) reported a lower prevalence of 0.02–0.03 per 10,000.

In conclusion, the prevalence of the condition in Europe was estimated to remain below 5 in 10,000 and was conservatively concluded to be 1 in 10,000 persons at the time of the review of the designation criteria. The COMP agreed with the methodology and figure proposed.

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 no European-wide accepted treatment algorithm for C3G and there are currently no products authorised for the treatment of this condition.

Like other glomerular diseases, disease management includes non-specific measures and RAS-inhibitors to manage proteinuria, hypertension, hyperlipidemia, oedema and other facets of glomerular and chronic kidney disease. According to the international practice guidance by KDIGO 2021, Mycophenolic Acid (MMF) and steroids are to be considered in C3G patients with moderate to severe disease, and if this fails, eculizumab should be considered. However, there are no randomised studies available to support this approach.

Despite these various measures, the prognosis of C3G is poor with 30 – 50% of patients progressing to end stage renal disease (ESRD) within 10 years of diagnosis. While renal transplantation is an option for these patients, the incidence of disease recurrence is high, and up to 50% patients lose their renal allografts. In general, matched donors are scarce, and particularly in the hereditary disease type, family members carrying the gene for C3G are not suitable candidates for donating a kidney.

The COMP concluded that there were no satisfactory methods available.

Significant benefit

Not applicable.

4. COMP position adopted on 28 February 2025

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 C3 glomerulopathy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1 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 the development of nephrotic syndrome and end-stage kidney disease leading to renal failure;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

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 Fabhalta, (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)), iptacopan, for treatment of C3 glomerulopathy (EU/3/18/2104) is not removed from the Community Register of Orphan Medicinal Products.