5 January 2024
EMA/OD/0000129455
EMADOC-1700519818-1197098
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Rystiggo (rozanolixizumab)
Treatment of myasthenia gravis
EU/3/20/2272

Sponsor: UCB Pharma

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

© European Medicines Agency, 2024. Reproduction is authorised provided the source is acknowledged

Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Rozanolixizumab
Other name(s)	-
International Non-Proprietary Name	Rozanolixizumab
Tradename	-
Orphan condition	Treatment of myasthenia gravis
Sponsor's details:	UCB Pharma Allee De La Recherche 60 1070 Brussels Brussels-Capital Region Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	UCB Pharma
COMP opinion	19 March 2020
EC decision	22 April 2020
EC registration number	EU/3/20/2272
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Thalia Marie Estrup Blicher / Robert Porszasz
Applicant	UCB Pharma
Application submission	3 November 2022
Procedure start	1 December 2022
Procedure number	EMA/H/C/005824
Invented name	Rystiggo
Proposed therapeutic indication	Rystiggo is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive. Further information on the product can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Rystiggo
CHMP opinion	9 November 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Elisabeth Penninga
Sponsor's report submission	3 February 2023
COMP discussion	7-9 November 2023
COMP opinion	9 November 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 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 rozanolixizumab was considered justified based on early clinical data showing positive responses on myasthenia gravis specific outcome measures;
- the condition is life-threatening and chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Recurrent myasthenic crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment;
- the condition was estimated to be affecting approximately 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.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rozanolixizumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who were not stabilised under the standard treatment including immunosuppressants achieved improvement of myasthenia gravis symptoms. The Committee considered that this constitutes a clinically relevant advantage.

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 rozanolixizumab as an orphan medicinal product for the orphan condition: treatment of myasthenia gravis".

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

Myasthenia gravis is an autoimmune disorder characterised by a combination of weakness and fatigability of skeletal muscles, including ocular, bulbar, limb, and respiratory muscles. Weakness is the result of an IgG antibody mediated, T-cell dependent immunological reaction against proteins in the

postsynaptic membrane of the neuromuscular junction (NMJ) of skeletal muscles (nicotinic acetylcholine receptors [AChR] and/or receptor-associated proteins). Patients present with muscle weakness, which typically worsens with continued activity (fatigability) and improves on rest.

Antibodies are present at (neuromuscular junctions) NMJ, the site of pathology (Engel et al, 1979). About 80% to 90% of MG patients have detectable antibodies against the AChR (Ruff and Lisak, 2018; Guptill and Sanders, 2010). Another 3% to 7% of patients have antibodies directed against MuSK, another NMJ protein.

Myasthenia gravis is recognised by existing classification systems, including WHO ICD-11. It is well recognised and specific treatment guidelines exist in the public domain.

The condition has been previously accepted by the COMP and is appropriate for an orphan designation.

The approved therapeutic indication "*Rystiggo is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive*" falls within the scope of the designated orphan condition "treatment of myasthenia gravis".

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

MG is considered to be a chronically debilitating condition. MG has a significant negative impact on patient-reported quality of life and the persistent muscle weakness associated with the disease often interferes with patients' ability to engage in daily activities, including maintaining the demands of work, family, social functions, and physical activities (Paul 2008; Gilhus 2019). Patients also report feeling 'frustrated' with their condition and sometimes overwhelmed or depressed (Gilhus 2019). The chronic nature of MG requires patients to cope with fluctuating symptoms and often maintain life-long treatment with a multi-therapeutic regimen that may include acetylcholinesterase inhibitors, corticosteroids, and/or other IS drugs (Sanders 2016; Nowak 2018; Gilhus 2019). Patients also report that the side effects of these medications, such as weight gain, diarrhoea/GI upset, and headaches/migraines have a significant impact on their daily life.

MG is also considered to be a life-threatening condition. Approximately 15% to 20% of patients with MG experience myasthenic crisis in their lifetime, most often occurring within the first 2 years from onset of MG and which is associated with a period of pre-crisis motor worsening. Such a crisis may be attributable to some physiologic stress (Sudulagunta 2016; Bedlack 2002). Myasthenic crisis often leads to hospitalisation within an intensive care unit and to respiratory failure, requiring involuntary intubation to assist with breathing (Gilhus 2015). Myasthenic crisis is associated with an in-hospital mortality rate of 5% to 12% even with utilization of modern therapies and specialised neurologic intensive care; the most common causes of death are multi-organ failure due to sepsis and respiratory failure despite maximal care (Neumann 2020).

The COMP has previously accepted that the condition (myasthenia gravis) is chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing and life-threatening due to respiratory impairment.

Number of people affected or at risk

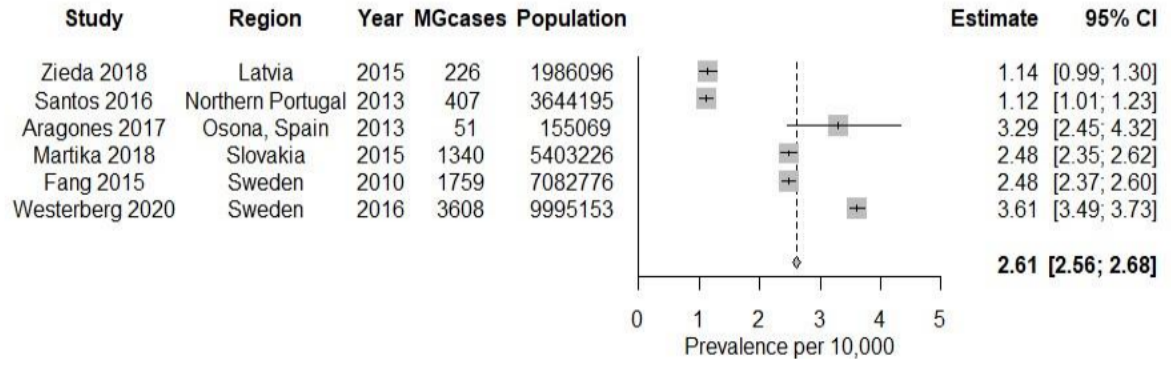
The sponsor proposes a prevalence estimate of 2.6 per 10,000 persons in the EU.

This estimate is higher than the one agreed by the COMP at time of initial orphan designation in April 2020 (EU/3/20/2272) which was 2 per 10,000 persons. At that time, prevalence of MG was based on published data from 2010 to 2020.

For the purpose of this orphan maintenance review, an updated literature search was conducted by the sponsor covering publications from 01 Jan 2010 to 31 Dec 2022. This identified 1 additional reference (Westerberg and Punga, 2020). Since MG is a chronic condition, no partial but a full prevalence is provided. Because of observed time-trend of prevalence of MG, the sponsor included studies published since 2010 to 2022 and conducted meta-analysis of reported prevalence for the period from 2010 until 2019 (Westerberg and Punga, 2020; Martinka et al, 2018; Zieda et al, 2018; Aragones et al, 2017; Santos et al, 2016; Fang et al, 2015). The pooled prevalence of MG as derived from 6 estimates (based on data from different EU countries) was 2.61 (95% CI: 2.56, 2.68) per 10,000 inhabitants, and crude estimates were all below the designation threshold. Furthermore, all published literature references identified the estimated prevalence rate of MG from databases and other sources ranging from 0.8 to 2.0 per 10,000, and an estimate of 2.0 per 10,000 was identified from existing positive opinions on Orphan Drug Designations for MG. Thus, an estimated prevalence of 2.61 per 10,000 inhabitants was assumed as the most conservative approach to estimate the current number of MG patients.

The sponsor further investigated the time-trends of MG prevalence which according to the sponsor appear to be rising across Europe over time (Aragonès et al, 2017; Pedersen et al, 2013; Zieda et al, 2018; Martinka et al, 2018; Carey et al, 2021).

Figure 1. Estimation of MG based on the prevalence of MG in the EU from 2010 to 2022



CI=confidence interval; ES=estimates; MG=myasthenia gravis
[1] Adjusted prevalence estimates were calculated using published estimates from 6 studies that reported estimates for prevalence dates 2010 to 2022. [2] Meta-analysis weighted by the population size in each study.

In summary, an MG prevalence of 2.61 per 10,000 was used as the most representative approach to calculate the current number of MG patients in the EU, and which was selected due to an apparent increasing trend of incidence and prevalence of MG is observed across Europe over time, which is most likely due to greater awareness of the disease, improved diagnostics and medical care, and potentially increased life expectancy. However, due to the small number of publications, and the small patient samples, it cannot be determined if this increase is indeed indicative of a general trend towards higher prevalence. Therefore, the previously accepted prevalence estimates of approximately 2 in 10,000 persons in the European Union (EU) are considered to be applicable by the COMP, for the time being.

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

The products listed in below Table 2 were identified as authorised for the treatment of MG in the EU:

Table 2. Products approved for the treatment of MG or gMG (EU)

Drug Name (Trade Name)	Marketing Authorization Holder	Authorized Indication
Cholinesterase inhibitor		
Distigminbromid (Ubretid®)	Takeda	Treatment of myasthenia gravis
Neostigmine bromide	Alliance Pharmaceuticals Ltd	Treatment of myasthenia gravis
Neostigmine methylsulfate (Prostigmine®)	Hameln Pharmaceuticals Ltd; Meda Pharma	Treatment of myasthenia gravis
Pyridostigmine bromide (Mestinon®)	Mylan Products Limited	Treatment of myasthenia gravis
Immunomodulating Treatment		
Glucocorticoids and other immunomodulating products		
Methylprednisolone (Metypred 16mg)	Orion Corporation	Conditions requiring systemic glucocorticoid treatment, especially autoimmune diseases. Neurological diseases (eg, multiple sclerosis, myasthenia gravis) (indication restricted to some national EU member states).
Prednisolone (Decortin® H)	Merck Serono GmbH	Certain forms of muscle paralysis (myasthenia gravis) (indication restricted to some national EU member states).
Non-steroidal immunosuppressive drug		
Azathioprine (Imurek®)	Aspen Pharma Trading Limited	Treatment of generalized myasthenia gravis.

Drug Name (Trade Name)	Marketing Authorization Holder	Authorized Indication
Rapid immunomodulating therapies		
IVIg (TEGELINE®) restricted to France only	LFB-BIOMEDICAMENTS	Treatment of acute myasthenia gravis flares
IVIg (Gamunex®) restricted to certain EU countries	Grifols	Severe acute exacerbations of MG in adults aged ≥18 years.
Biologics		
Efgartigimod alfa (Vyvgart®)	argenx	Indicated as add-on to standard therapy for the treatment of adult with gMG who are anti-AChR antibody positive.
Eculizumab (Soliris®)	Alexion Pharmaceuticals, UK Ltd	Indicated in adults for the treatment of refractory gMG in patients who are AChR antibody positive.
Ravulizumab (Ultomiris®)	Alexion Europe SAS	Indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody positive

EU=European Union; gMG=generalized myasthenia gravis; =IVIg=intravenous immunoglobulin; MG=myasthenia gravis
Drug products are listed in alphabetical order according to active substance. Only one representative is listed for generics; other generic products may be authorized in different European countries.

In general, use of approved as well as off-label MG therapies aim to either directly alleviate symptoms or to dampen the underlying immunopathology causing the disease (Farrugia and Goodfellow, 2020). As such, current standard of care therapy for MG primarily focuses on symptom alleviation with acetylcholinesterase inhibitor (AChEI), or non-specifically suppressing the autoimmune response with corticosteroids or nonsteroidal immunomodulating drugs (NSISTs).

The mainstays of the routine management of MG are defined in international consensus guidelines, most recently by the American Academy of Neurology (Narayanaswami et al, 2021). This guidance includes the following recommendations:

- The AChE inhibitor pyridostigmine should be part of the initial treatment in most patients with MG.
- Corticosteroids or NSIST therapy for patients who have not met treatment goals after an adequate trial of pyridostigmine. NSISTs may be used alone when corticosteroids cannot be used. NSISTs that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus.
- Patients with refractory MG may be treated with chronic IVIg and chronic plasmapheresis/plasma exchange (PLEX) as maintenance therapy, cyclophosphamide, rituximab.

It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Patients must be monitored for potential adverse effects and complications from immunosuppression and changing treatment may be required.

Biologics have added to the more targeted treatment options for gMG, with eculizumab (Soliris) being a first-in-class humanized mAb targeting the terminal complement complex, blocking the enzymatic cleaving of complement 5 (C5) and thereby preventing the activation of the complement complex. Eculizumab should be considered in the treatment of severe, refractory, AChR-Ab+ generalized MG (Narayanaswami et al., 2021). Due to lack of complement involvement in the pathophysiology of anti-

MuSK+ patients with gMG, this difficult-to-treat subgroup of patients does not benefit from C5 inhibitor treatment.

The most recent addition to the MG treatment regimen has been the introduction of efgartigimod (Vyvgart), an IgG1 Fc fragment targeting neonatal Fc receptor leading to reduced overall IgG recycling, and ravulizumab (Ultomiris), a recombinant mAb that inhibits terminal complement activation at the C5 protein. Both products are indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive. As these products were only authorised in 2022, they are not reflected in the the International Consensus Guidance for Management of Myasthenia Gravis by Narayanaswami et al, (2021).

A significant unmet medical need persists for MuSK Ab+ MG patients.

Considering that Rystiggo is intended as an add-on to standard of care therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are not only anti-acetylcholine receptor (AChR) but also anti-muscle-specific tyrosine kinase (MuSK) antibody positive, no satisfactory methods are identified for the purpose of this procedure. Accordingly, the COMP concluded in their opinion that no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Rystiggo.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 9 November 2023

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 myasthenia gravis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2 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 muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing. Recurrent myasthenic crisis can also affect muscles that control breathing, resulting in life-threatening respiratory failure;
- 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 Rystiggo.

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 Rystiggo, rozanolixizumab for treatment of myasthenia gravis (EU/3/20/2272) is not removed from the Community Register of Orphan Medicinal Products.