26 August 2019
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Soliris (eculizumab)
Treatment of neuromyelitis optica spectrum disorders
EU/3/13/1185
Sponsor: Alexion Europe SAS

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	
Active substance	Eculizumab
International Non-Proprietary Name	Eculizumab
Initial orphan condition	Treatment of neuromyelitis optica
Amended orphan condition (at time of review of criteria for orphan designation)	Treatment of neuromyelitis optica spectrum disorders
Pharmaceutical form	Concentrate for solution for infusion
Route of administration	Intravenous route
Pharmaco-therapeutic group (ATC Code)	L04AA25
Sponsor's details:	Alexion Europe SAS 1-15 avenue Edouard Belin 92500 Rueil Malmaison France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Alexion Europe SAS
COMP opinion date	11 July 2013
EC decision date	5 August 2013
EC registration number	EU/3/13/1185
Post-designation procedural history	
Change of designated condition COMP opinion date	21 March 2019
Change of designated condition EC decision date	24 April 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	J. Jiménez, A. Moreau
Applicant	Alexion Europe SAS
Application submission date	9 January 2019
Procedure start date	27 January 2019
Procedure number	EMA/H/C/000791/II/0105
Invented name	Soliris
Therapeutic indication	Treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease. Further information on Soliris can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/summaries-opinion/soliris
CHMP opinion date	25 July 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	D. Matusevicius, M. Hoffmann
Sponsor's report submission date	8 February 2019
COMP discussion	15-17 April 2019
COMP opinion date	26 July 2019

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 2013 was based on the following grounds:

The sponsor Alexion Europe SAS submitted on 23 May 2013 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing eculizumab for treatment of neuromyelitis optica (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

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 eculizumab was considered justified based on preliminary clinical data showing a reduction in the number of relapses in patients treated with the product;
- the condition is chronically debilitating due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, and central visual loss accompanied by ocular pain, and life-threatening with 5-year mortality reported as high as 30%;
- the condition was estimated to be affecting approximately 0.4 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 eculizumab, as an orphan medicinal product for the orphan indication: treatment of neuromyelitis optica.

2.2. Amendment of an existing orphan medicinal product designation

The COMP opinion that was the basis for the amendment of the orphan medicinal product designation in 2019 was based on the following grounds:

Alexion Europe SAS, the sponsor of the orphan designation of a medicinal product containing eculizumab for treatment of neuromyelitis optica spectrum disorder, submitted on 20 December 2018 an application for amendment of the existing designation. The proposed amended indication is: neuromyelitis optica spectrum disorders. The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

For the purpose of amendment of an existing designation, the Committee for Orphan Medicinal Products (COMP) considered that the amended condition proposed by the sponsor should be renamed

as "treatment of neuromyelitis optica disorders" (hereinafter referred to as "the condition") based on the current international diagnostic consensus (Wingerchuk et al., Neurology 2015; 85:1-13).

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 eculizumab was considered justified based on clinical data supporting a delay of relapse in treated patients;
- the condition is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality;
- the condition was estimated to be affecting approximately 0.4 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 amendment of the designation as follows: the medicinal product containing eculizumab for the orphan indication: treatment of neuromyelitis optica spectrum disorders.

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

The target condition is an inflammatory disorder of the CNS characterized by immune-mediated demyelination and axonal damage. It is characterised by the occurrence of events of myelitis and optic neuritis with variable and incomplete recovery that result in permanent impairment. The myelitis typically affects an area greater than three vertebral segments long, and causes severe paraplegia, sensory loss and bladder dysfunction.

In 2015, the International Panel for NMO Diagnosis developed revised diagnostic criteria for the neuromyelitis optica (Wingerchuk, Neurology 2015 Jul 14; 85(2): 177–189). Importantly, the new nomenclature qualifies the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-antibodies). Accordingly, the applicant had submitted before the MAA application, a request for amendment of the orphan designation "treatment of neuromyelitis optica" to "treatment of neuromyelitis optica spectrum disorder".

This current consensus describes 6 core clinical characteristics: optic neuritis, acute myelitis, area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting), acute

brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with typical MRI findings, symptomatic cerebral syndrome with MRI findings. In general for diagnostic purposes, at least 2 core characteristic (for the NMOSD without autoantibodies) or 1 core and autoantibody are described (Wingerchuk, Neurology 2015 Jul 14; 85(2): 177–189).

The extension of Indication to include "treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease" falls within the proposed amendment of the orphan indication to "treatment of Neuromyelitis Optica Spectrum Disorders". It is also to be noted that as reflected in the summary report of the initial procedure, the NMO designation encompassed both definite NMO cases and NMOSD cases.

Intention to diagnose, prevent or treat

The intention to treat the condition was accepted based on the positive benefit/risk assessment of the CHMP (see EPAR of Soliris).

Chronically debilitating and/or life-threatening nature

The applicant discusses the relapses in affected patients, resulting in severe, permanent neurologic impairment. In the majority of cases (approximately 80%), relapses occur by 2-3 years after the index event. Clinical attacks progress over days with varying, usually incomplete, recovery over the next few months. Ambulatory and visual deficits affect most patients (Oh and Levy, Neurology Research International Volume 2012, Article ID 460825).

A decrease in mortality compared to what has been initially reported in the literature, is acknowledged by the applicant, which is attributed to the use of immunosuppressive treatment. It is at the same time noted that the annual mortality rate of patients with NMOSD remains at nearly 10% ((9.4% mortality over 99 months for a group of aquaporin-4 antibody-seropositive patients) (Kitley et al, Brain 2012: 135; 1834–1849)).

The COMP acknowledged that NMOSD is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality.

Number of people affected or at risk

After conducting a literature and database search, the sponsor is proposing a 0.44 per 10,000 prevalence figure, based on population-based study in Denmark. This study estimated the incidence and prevalence of NMO in a predominantly Caucasian population based on the Wingerchuk 2006 criteria, drawing from the 4 neurology and 3 ophthalmology departments in the Region of Southern Denmark. The prevalence was estimated to be 4.4 per 100,000 ((95% CI 3.1–5.7) (Asgari, Neurology 2011;76:1589–1595).

Several other studies are also cited in the sponsor's application and the prevalence for NMOSD ranged from 0.52 to 4.4 per 100,000. In a study by Cossburn et al (Eur J Neurol. 2012;19(4):655-9) prevalence was determined to be 1.96 per 100,000 persons and was considered as a good estimate of the prevalence of diagnosed NMOSD in Caucasians.

The study by Asgari et al, was considered to be reporting the highest and most conservative figure from the list of epidemiological studies identified by the sponsor. Therefore, it was acknowledged that the number of affected patients is at the time of maintenance described in the literature to be up to approximately 0.4 in 10,000 people in the EU.

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 no authorised products for the sought condition that have been identified by the sponsor.

The off-label use of systemic immunosuppressants in the condition has been further discussed: the literature has described courses of glucocorticoids for the treatment of attacks in patients, who are not responding to therapeutic plasma exchange (Kleiter et al. Ann Neurol. 2016 Feb;79(2):206-16. Epub 2015 Nov 26). For the prevention of attacks, chronic use of immunosuppressants such as azathioprine, mycophenolate and rituximab has been suggested (EMA/CHMP/SAWP/712652/2014). The COMP does not consider off-label use of medicinal products for the demonstration of significant benefit.

In conclusion, the COMP confirmed that there are currently no satisfactory methods for the treatment of the condition.

Significant benefit

In the absence of satisfactory methods, including authorised medicinal products for the treatment of NMSOD, a significant benefit justification is not required.

4. COMP position adopted on 26 July 2019

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 neuromyelitis optica spectrum disorders (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to manifestations such as visual impairment, paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality;
- there is, at present, no satisfactory treatment that 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 Soliris (eculizumab), EU/3/13/1185 for treatment of neuromyelitis optica spectrum disorders is not removed from the Community Register of Orphan Medicinal Products.