28 October 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Adakveo (crizanlizumab, humanised monoclonal antibody targeting P-selectin)
Treatment of sickle cell disease
EU/3/12/1034

Sponsor: Novartis Europharm Limited

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 substances(s) at the time of orphan designation	Humanised monoclonal antibody targeting P-selectin
Other name(s)	SEG101; SelG1
International Non-Proprietary Name	Crizanlizumab
Tradename	Adakveo
Orphan condition	Treatment of sickle cell disease
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Quintiles Ireland Ltd
COMP opinion date	11 July 2012
EC decision date	9 August 2012
EC registration number	EU/3/12/1034
Post-designation procedural history	
Transfer of sponsorship	- Transfer from Quintiles Ireland Ltd to Novartis Europharm Ltd – EC decision of 9 March 2017 - 2nd transfer from Novartis Europharm Limited, United Kingdom, to Novartis Europharm Limited, Ireland - EC decision of 8 May 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	M. Stain / T. Lapveteläinen
Applicant	Novartis Europharm Limited
Application submission date	29 May 2019
Procedure start date	20 June 2019
Procedure number	EMA/H/C/004874
Invented name	Adakveo
Therapeutic indication	Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate Further information on Adakveo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Adakveo
CHMP opinion date	23 July 2020

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	A. Magrelli / I. Barisic
EMA scientific officer	Stylianos Tsigkos
Expert	N/A
Sponsor's report submission date	8 July 2019
COMP discussion, adoption of list of questions (via written procedure)	16-18 June 2020, 26 June 2020
Oral explanation cancellation	9 September 2020
COMP opinion date	10 September 2020

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2012 designation was based on the following grounds:

The sponsor Quintiles Ireland Ltd, submitted an application for designation as an orphan medicinal product to the European Medicines Agency for humanised monoclonal antibody targeting P-selectin for treatment of sickle cell disease.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- for the purpose of orphan designation, the COMP considered that the active ingredient should be renamed as "humanised monoclonal antibody against P-selectin";
- sickle cell disease (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made based on published literature studies;
- the condition is chronically debilitating and life-threatening, in particular due to anaemia, vaso-occlusive ischemic incidences, bacterial infections resulting in reduced survival;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that humanised monoclonal antibody against P-selectin may be of significant benefit to those affected by the condition. This is based on a novel mechanism of action that may result in reduction of vaso-oclusive crises and related complications. This is supported by preclinical data in valid models of the proposed condition as applied for.

The COMP recommends the designation of this medicinal product, containing humanised monoclonal antibody against P-selectin, as an orphan medicinal product for the orphan indication: treatment of sickle cell disease.

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

Sickle cell disease (SCD) is a haemoglobinopathy caused by a single point mutation in the 6th codon of the β globin disease, that leads to substitution of glutamic acid for valine. Vaso-occlusion, haemolytic anaemia and vasculopathy are the hallmarks of SCD pathophysiology. (Pinto et al Intern Emerg Med. 2019 Oct;14(7):1051-1064). Although current management of patients can dramatically improve survival and quality of life, our understanding of the role of genetic and nongenetic factors in explaining the remarkable phenotypic diversity is still limited (Copi et al, NEJM 2017 Apr 20;376(16):1561-157). No classification changes have been reported since the orphan designation, and the condition is still a distinct medical entity valid for the purposes of the orphan framework.

The therapeutic indication: "Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate" falls entirely within the orphan designation "treatment of sickle cell disease".

Intention to diagnose, prevent or treat

The medical plausibility is considered confirmed based on the positive benefit/risk assessment of the CHMP, please see EPAR.

Chronically debilitating and/or life-threatening nature

The COMP considered that condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival. This view is retained for this procedure.

Number of people affected or at risk

The sponsor is proposing a less than 2 per 10,000 prevalence based on different methods. Firstly, based on a literature population-based studies, referencing in particular the studies below:

Table 1. Adopted from the sponsor submission documents.

Publication	Country/Region	Prevalence (per 10,000 Population)
Voskaridou et al. (2012)	Greece	Estimated[a]: 2010: 0.97
Peters et al. (2010)	The Netherlands	Estimated: 2003: 1.94 in the paediatric population
Kyrri et al. (2009)	Cyprus	Estimated: 1986: 0.9
Kohne and Kleihauer (2010)	Germany	Estimated[a]: 2007: 0.38
Gulbis et al. (2008)	Belgium	Estimated: 2006: 0.32
Cela et al. (2017)	Spain	Estimated[a]: 2015: 0.13

Secondly, estimates of birth prevalence were also given, with results of six studies conducted in England, Germany, France, and Spain calculated a prevalence from birth ranging from 0.3 (Spain) to 5.4 (England) per 10,000 individuals. It was considered that the usefulness of such data is however limited, as the birth rate does not appear to have been taken into consideration, for the derivation of an actual prevalence figure.

In a third methodology, the sponsor produced an estimate from estimated sickle haemoglobin (HbS) gene frequencies, and the prevalence was calculated as 1.92 per 10,000 individuals by applying the estimates from Modell and colleagues (Modell et al., Scand J Clin Lab Invest 2007;67(1):39-69) to the targeted European population (Eurostat, 2007).

Finally, databases have been consulted, including an estimation of Sickle Cell Disease from the National Haemoglobinopathies Registry in the UK reporting as 1.91 per 10,000 individuals, based on over 55 centres with registered patients. An additional reference to Orphanet (Orphanet report January 2018) with an HbSS prevalence of 2.2 per 10,000 was also put forward.

The COMP considered that the exercise of estimating the number of affected individuals was difficult, due to the heterogeneity across different countries and recent population moves; however, it was agreed that in line with the above different approaches the number of affected individuals would be less than 2 in 10,000.

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 only approved medicinal products (Siklos, Xromi) in the EU for SCD contain the active substance hydroxyurea (HU), also known as hydroxycarbamide:

- Siklos is indicated for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome.
- Xromi is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age.

Available symptomatic treatments of VOCs include pain management (non-steroidal anti-inflammatory drugs, opioids and other analgesics), and with other supportive care, such as hydration with IV fluids, oxygen therapy, and/or blood transfusions (Bender and Hobbs 1993, Rees et al 2010) cannot prevent or stop progression of a VOC. Haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for patients with SCD with only a limited number of patients being eligible.

Significant benefit

The sponsor has received protocol assistance late in the development, where the COMP agreed with the appropriateness of the main study design and noted that the subgroup analysis of the HU patients will be of particular importance to justify the significant benefit over HU.

In relation to the issue of significant benefit, the sponsor made particular reference to the final authorised therapeutic indication, which includes the following populations: a) as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC), and b) as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

In accordance with this indication, the SUSTAIN study results were examined in two particular subgroups: in patients receiving the product as an add-on to HU, (table 2-1 below, adopted from the sponsor's documents) and in patient without HU treatment (Table 2-2).

Table 2-1 Results from Study A2201 (SUSTAIN) – VOC related endpoints, patients treated with HU/HC

	Crizanlizumab 5 mg/kg (N=42)	Placebo (N=40)	Change vs placebo	Treatment difference estimate (95% CI)
Primary endpoint				
Annual rate of VOC*	2.43	3.58	−32.1%	HL=−1.01 (−2.44, 0.00)
Other efficacy endpoints				
Number of patients with no VOC leading to a healthcare visit**	14 (33%)	7 (18%)	NA	OR=2.36 (0.84, 6.65)
Time to 1st VOC leading to a healthcare visit (months)***	2.43	1.15	NA	HR=0.58 (0.35, 0.96)
Annual rate of uncomplicated VOC*	1.74	3.13	−44.4%	HL=−1.01 (−2.62, 0.00)

* Standard median, HL = Hodges-Lehmann absolute median difference between treatment arms (95% CI)

** n(%), OR = Odds Ratio (95% CI)

*** Estimated Kaplan-Meier median, HR = Hazard-ratio (95% CI) calculated based on Cox regression analysis with HU therapy (yes, no), categorized crises history (2-4, 5-10), and treatment as covariates

Table 2-2 **Results from Study A2201 (SUSTAIN) – Patients not receiving HU/HC**

	Crizanlizumab 5 mg/kg (N=25)	Placebo (N=25)	Change vs placebo	Treatment difference estimate (95% CI)
Primary endpoint				
Annual rate of VOC*	1.00	2.00	−50.0%	HL=−1.02 (−2.00, 0.00)
Other efficacy endpoints				
Number of patients with no VOC leading to a healthcare visit**	10 (40%)	4 (16%)	NA	OR=3.50 (0.92, 13.31)
Time to 1st VOC leading to a healthcare visit (months)***	5.68	2.86	NA	HR=0.39 (0.20, 0.76)
Annual rate of uncomplicated VOC*	0.98	1.98	−50.5%	HL=-1.00 (−1.98, 0.00)

* Standard median, HL = Hodges-Lehmann absolute median difference between treatment arms (95% CI)
** n(%), OR = Odds Ratio (95% CI)
*** Estimated Kaplan-Meier median, HR = Hazard-ratio (95% CI) calculated based on Cox regression analysis with HU therapy (yes, no), categorized crises history (2-4, 5-10), and treatment as covariates

With reference to the above tables, a consistent trend across different VOC-related endpoints, in both subgroups analysed, was observed. As per the main endpoint, a reduction of approximately 30% in the annual rate of VOC was reported in treated patients as an add-on to hydroxyurea, while in patients who did not receive hydroxyurea the reduction was approximately 50%.

Overall, the COMP accepted that the therapeutic indication of Adakveo, covers additional populations compared to hydroxyurea. This was considered to be a clinically relevant advantage, justifying the criterion of significant benefit.

4. COMP position adopted on 10 September 2020

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 sickle cell disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Adakveo may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data that support use of crizanlizumab as an add-on to hydroxyurea, or in patients for whom hydroxyurea is inappropriate or inadequate. This constitutes a clinically relevant advantage.

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 Adakveo, humanised monoclonal antibody targeting P-selectin, crizanlizumab for treatment of sickle cell disease (EU/3/12/1034) is not removed from the Community Register of Orphan Medicinal Products.