22 November 2018
EMA/811424/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Poteligeo (mogamulizumab)

Treatment of cutaneous T-cell lymphoma

EU/3/16/1756 (EMA/OD/091/16)

Sponsor: Kyowa Kirin Holdings B.V.

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Product and administrative information

Product	
Active substance	Mogamulizumab
International Non-Proprietary Name	Mogamulizumab
Orphan indication	Treatment of cutaneous T-cell lymphoma
Pharmaceutical form	Concentrate for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L01XC25
Sponsor's details:	Kyowa Kirin Holdings B.V. Bloemlaan 2 2132NP Hoofddorp The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kyowa Kirin Limited
COMP opinion date	08 September 2016
EC decision date	14 October 2016
EC registration number	EU/3/16/1756
Post-designation procedural history	
Transfer of sponsorship	Transfer from Kyowa Kirin Limited to Kyowa Kirin Holdings B.V.– EC decision of 03 August 2018
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Paula Boudewina van Hennik, Daniela Melchiorri
Applicant	Kyowa Kirin Holdings B.V.
Application submission date	06 October 2017
Procedure start date	26 October 2017
Procedure number	EMA/H/C/004232/0000
Invented name	Mogamulizumab
Therapeutic indication	Poteligeo is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy Further information on can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/poteligeo
CHMP opinion date	20 September 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	B. Bloechl-Daum - J. Ersbøll
Sponsor's report submission date	03 May 2018
COMP discussion and adoption of list of questions	11-13 September 2018
Oral explanation	11 October 2018
COMP opinion date	11 October 2018

2. Grounds for the COMP opinion at the designation stage

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing mogamulizumab was considered justified based on preclinical data showing reduction of tumour size, and on preliminary clinical data;
- the condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The overall five-year survival rates vary between 24% and 68% according to the subtype of cutaneous T-cell lymphoma;
- the condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

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

At the designation stage in 2006, cutaneous T-cell lymphomas (CTCL) were considered a heterogeneous subgroup of non-Hodgkin's lymphoma with the 2 main subtypes being mycosis fungoides (MF) and Sézary syndrome (SS). In the most updated version of WHO classification, several types cutaneous T-cell lymphomas are described under the "mature T/NK cell neoplasms" (Swerdlow, et al, 2016, Blood 127(20): 2375-2390).

In the ESMO clinical practice guidelines reflecting WHO-EORTC classificatoin, Cutaneous T-cell lymphomas include mycosis fungoides and its variants (folliculotrophic MF, pagetoid reticulosis, granulomatous slack skin), Sezary Syndrome, primary cutaneous CD30+ lymphoproliferative disorders (Primary cutaneous anaplastic large cell lymphoma, Lymphomatoid papulosis), Subcutaneous panniculitis-like T cell lymphoma , Extranodal NK/T cell lymphoma nasal-type , as well as primary cutaneous peripheral T cell lymphoma-not otherwise specified (Primary cutaneous γ/δ T cell lymphoma,Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma, Primary cutaneous acral CD8+ T cell lymphoma, Primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder) (Willemze, Ann Oncol.(2018); 00: 1–11). All of the above entities can thus be considered as covered by the orphan indication.

The proposed therapeutic indication "POTELIGEO is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy" falls entirely within the scope of the designated orphan indication "treatment of cutaneous T-cell lymphoma".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition is considered justified.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes in the seriousness of the condition compared to the time of orphan designation.

The COMP has acknwledged that CTCL is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The overall five-year survival rates vary between 24% and 68% according to the subtype of cutaneous T-cell lymphoma.

Number of people affected or at risk

The applicant performed a literature and database search and produced an incidence ranging from 0.052-0.29/10,000/year based on databases and a range of 0.047-0.14/10,000/year based on published literature. The applicant was invited by the COMP to perform the exercise according to the "points to consider on the calculation of prevalence" document and estimate the point prevalence at the time of the review of the criteria.

In response to the raised issue by the COMP, the sponsor assumed a 20 years duration of the disease (Agar et al, J Clin Oncol. 2010, 28(31):4730-9.) and used a 0.13 yearly incidence (as a mean of the lower and upper figures above) to produce an estimate of 2.6 per 10,000.

This was considered acceptable for the purpose of the maintenance procedure and in line with previous COMP considerations.

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

As per knowledge of the COMP, currently authorised products in the EU for treatment of CTCL include bexarotene, bleomycin, dexamethasone, interferon alpha, chlormethine, brentuximab vedotin. The applicant pointed out in particular the following:

- Roferon-A authorisation states that "Interferon may be active in patients who have progressive disease and who are refractory to, or unsuitable for, conventional therapy" (UK Roferon SPC 2016).
- Targretin (bexarotene) is authorised for the skin manifestations of advanced stage CTCL in adult patients refractory to at least one systemic treatment (Targretin SPC 2015).
- Ledaga (chlormethine) was authorised in 2017 for the topical treatment of MF-type CTCL in adult patients (Ledaga SPC 2017).
- Adcetris (brentuximab) is authorised for the treatment of adult patients with CD30+ CTCL after at least 1 prior systemic therapy (Adcetris SPC 2018).

Moreover, there are 2018 treatment guidelines of ESMO for primary cutaneous lymphomas, (Annals of Oncology 29 (Supplement 4): iv30–iv40, 2018) giving summary recommendations for MF and SS. In particular for refractory or second line treatments, gemcitabine, liposomal doxorubicin and alemtuzumab (the latter for SS), are also mentioned as accepted standards, and therefore they can be of relevance for the justification of significant benefit.

Significant benefit

The sponsor produced three types of arguments to justify significant benefit:

a) expectations from the mechanism of action of the product

b) responses in patients that have failed available therapies and;

c) an implicit argument of improved safety ("Mogamulizumab has a favourable safety profile in subjects with CTCL. The majority of TEAEs are manageable".)

Of those arguments, the first one was not considered acceptable per se in the absence of data demonstrating the assumed improved effects, while the third one was not elaborated on versus the other products. However, the second argument was considered meriting further discussion, and the sponsor was invited by the COMP to provide a clinical data-driven comparative discussion versus the authorised treatments, to justify either a clinically relevant advantage or a major contribution to patient care.

In response sponsor elaborated on the prior therapies of the patients included in the pivotal Marketing Authorisation study, with more than 60% of patients enrolled having failed at least 3 prior systemic treatments administered, and some having failed up to 18. It was stated that in the EU patients prior therapies included Bexarotene-Oral, Interferon-alpha, Methotrexate, PUVA, ECP, Gemcitabine/Gemcitabine Regimen, Topical Steroid Phototherapy, Doxorubicin HCL Liposome, Retinoid, Carmustine, CHOP/CHOP like Regimens, Nitrogen Mustard, Oral Steroid, Alemtuzumab, Brentuximab, HDAC Inhibitors. The sponsor provided in particular one table describing the responses seen in the 0761-010 study as per previous treatment. Confirmed ORR, as measured by Investigator Assessment (IA), in the ITT population of Study 0761-010 by prior CTCL therapies commonly used in Europe is summarized in the table below:

Table 1. Sourced from the sponsor's supplementary responses.

	Mogamulizumab N=186		**Vorinostat N=186**		**Treatment Comparison**	
Prior CTCL Therapy	**N**	**ORR n (%)**	**N**	**ORR n (%)**	**Risk Difference (M vs. V)**	**p-value**
Bexarotene Oral	107	29 (27.1)	110	4 (3.6)	23.5	<0.0001
Interferon-alpha	81	27 (33.3)	94	4 (4.3)	29.1	<0.0001
PUVA	80	17 (21.3)	63	5 (7.9)	13.3	0.0305
Methotrexate	69	22 (31.9)	73	4 (5.5)	26.4	<0.0001
Gemcitabine	37	6 (16.2)	25	1 (4.0)	12.2	0.1030
Brentuximab Vedotin	16	4 (25.0)	4	0	25.0	0.2568
ECP	71	39.4	65	4.6	34.8	

Based on this information, the COMP acknowledged that there are documented responses in patients who have failed the authorised treatments covering the proposed population. It was further considered that in particular in patients who have failed multiple lines of previous treatments, the product offers a clinical relevant advantage.

In particular effects in non-cutaneous lesions were considered relevant, taking into consideration that the assessment of responses related to multiple compartments of disease (such as skin, blood and lymph nodes). With reference to the secondary analyses in the CHMP assessment report, the response rates (confirmed CR + PR, %) by compartment (mogamulizumab vs vorinostat) were for blood 66.9 vs 18.4 (p<0.0001) for skin lesions 41.9 vs 15.6 (p<0001) and for lymph nodes 15.4 vs 3.8 (p=0.0008) (table below).

Table 2. Response during randomised treatment period in study 0761-010 (intent-to-treat). Source: CHMP AR,

	Mogamulizumab N=186	**Vorinostat N=186**
Overall response rate (confirmed CR + PR, %)	28.0	4.8
95% CI	(21.6, 35.0)	(2.2, 9.0)
P-valuea	<.0001	
Duration of response (months)		
Median (95% CI)	14.1 (9.4, 19.2)	9.13 (4.7,-)
Response by compartment		
Blood	n=124	n=125
Response rate (confirmed CR + PR, %)	66.9	18.4
95% CI	(57.9, 75.1)	(12.0, 26.3)
P-value[a]	<0.0001	
Skin	n=186	n=186
Overall response rate (confirmed CR + PR, %)	41.9	15.6
95% CI	(34.8, 49.4)	(10.7, 21.6)
P-valuea	<.0001	
Lymph nodes	n=136	n=133
Overall response rate (confirmed CR + PR, %)	15.4	3.8
95% CI	(9.8, 22.6)	(1.2, 8.6)
P-valuea	0.0008	
Viscera	n=6	n=4
Overall response rate (confirmed CR + PR, %)	0	0
95% CI	(0.0, 45.9)	(0.0, 60.2)

Based on the above data, the COMP considered that the responses in patients who have failed multiple previous therapies and covering multiple compartments of the disease constitute a clinically relevant advantage.

4. COMP position adopted on 11 October 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of cutaneous T-cell lymphoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 2.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The condition is life-threatening with five-year survival rates varying between 24% and 68% according to the subtype of cutaneous T-cell lymphoma;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Poteligeo may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data documenting responses in multiple compartments of disease (such as skin, blood and lymph nodes) in patients who have previously failed multiple lines of available treatments. The COMP considered that 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 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 Poteligeo, Mogamulizumab, EU/3/16/1756 for treatment of cutaneous T-cell lymphoma is not removed from the Community Register of Orphan Medicinal Products.