



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/OD/0000003161
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Polivy (polatuzumab vedotin)
Treatment of diffuse large B-cell lymphoma
EU/3/18/2013 (EMA/OD/0000003161)
Sponsor: Roche Registration GmbH

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	Polatuzumab vedotin
International Non-Proprietary Name	Polatuzumab vedotin
Orphan condition	Treatment of diffuse large B-cell lymphoma
Pharmaceutical form	Powder for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L01XC37
Sponsor's details:	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Roche Registration Limited
COMP opinion date	15 March 2018
EC decision date	16 April 2018
EC registration number	EU/3/18/2013
Post-designation procedural history	
Transfer of sponsorship	Transfer from Roche Registration Limited to Roche Registration GmbH – EC decision of 25 July 2018
Marketing authorisation	
Rapporteur / Co-rapporteur	A. Moreau / J. Mueller-Berghaus
Applicant	Roche Registration GmbH
Application submission date	20 December 2018
Procedure start date	25 January 2019
Procedure number	EMA/H/C/004870
Invented name	Polivy
Therapeutic indication	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. Further information on Polivy can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/polivy
CHMP opinion date	14 November 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	F. Naumann-Winter / E. Johanne Rook
Sponsor's report submission date	28 January 2019
COMP discussion and adoption of list of questions	18-20 June 2019
COMP discussion and revision of the list of questions	8-10 October 2019
Oral explanation	4 December 2019
COMP opinion date	5 December 2019

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing polatuzumab vedotin was considered justified based on clinical observations supporting improved survival in relapsed/refractory patients when the proposed treatment is added on to other existing treatments;
- the condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as approximately 25% for high risk patients;
- the condition was estimated to be affecting approximately 4.3 in 10,000 persons in the European Union, at the time the application was made;
- 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 polatuzumab vedotin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and preliminarily clinical observations in relapsed/refractory patients supporting add-on effects in terms of clinical response and survival, when the product is combined with other existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin's lymphoma (NHL) accounting for 35% of NHL and 80% of aggressive lymphomas.

The approved therapeutic indication "Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant." falls within the scope of the designated orphan condition "treatment of diffuse large B-cell lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP on the basis of the submitted evidence including pivotal trial GO29365. Polivy received a conditional marketing authorisation. For a full discussion of the results and the justification of the conditional marketing authorisation please be referred to the European Public Assessment Report of Polivy.

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review DLBCL was presented to the COMP to remain chronically debilitating and life-threatening disease with a median survival of less than one year if left untreated. Approximately 60% of patients may be cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), the current standard of care. The clinical course can be debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anaemia, and thrombocytopenia

The COMP concluded that the condition remains chronically debilitating and life-threatening with 5-year survival rates reported as low as approximately 25% for high risk patients.

Number of people affected or at risk

At the time of designation, the prevalence (P) was agreed to be approximately 4.3 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 4.54 per 10,000. This estimate has been derived by using the formula $P=I*D$ (incidence * duration). For the calculation, the most recent 2018 incidence figures of NHL have been used from the Globocan database. It was assumed that 47.8% of NHL would account for DLBCL. The disease duration was estimated to be 5 years. These estimates have been reported by Smith and colleagues based on data from the Hematologic Malignancy Research Network (HMRN), which covers a limited area in the United Kingdom. The figures and estimates of all EU countries have been presented (table 1) with an EU wide prevalence estimate of 4.54 per 10,000. The COMP concluded that the currently available epidemiological data sufficiently demonstrate that the prevalence of DLBCL remains below the threshold. The COMP will continue to closely monitor the prevalence of DLBCL.

Table 1. DLBCL prevalence as reported in the dossier

Country	Gender	Population in 2018 (in 1000)	NHL incidence count for 2018	DLBCL incidence count for 2018	DLBCL incidence rate per 10k per yr in 2018	DLBCL prevalence per 10k in 2018
Austria	Male	4,339	714	341	0.79	3.93
	Female	4,509	616	294	0.65	3.27
Belgium	Male	5,627	1536	734	1.30	6.52
	Female	5,808	1129	540	0.93	4.65
Bulgaria	Male	3,428	314	150	0.44	2.19
	Female	3,630	285	136	0.38	1.88
Croatia	Male	1,995	274	131	0.66	3.28
	Female	2,135	260	124	0.58	2.91
Cyprus	Male	417	83	40	0.95	4.76
	Female	441	89	43	0.96	4.82
Czech Rep.	Male	5,213	822	393	0.75	3.77
	Female	5,393	864	413	0.77	3.83
Denmark	Male	2,882	748	358	1.24	6.20
	Female	2,916	555	265	0.91	4.55

Country	Gender	Population in 2018 (in 1000)	NHL incidence count for 2018	DLBCL incidence count for 2018	DLBCL incidence rate per 10k per yr in 2018	DLBCL prevalence per 10k in 2018
Estonia	Male	617	119	57	0.92	4.61
	Female	699	95	45	0.65	3.25
Finland	Male	2,721	711	340	1.25	6.25
	Female	2,803	610	292	1.04	5.20
France	Male	32,624	8627	4124	1.26	6.32
	Female	34,625	6118	2924	0.84	4.22
Germany	Male	40,893	9480	4531	1.11	5.54
	Female	42,303	7593	3629	0.86	4.29
Greece	Male	5,179	742	355	0.68	3.42
	Female	5,498	487	233	0.42	2.12
Hungary	Male	4,678	774	370	0.79	3.95
	Female	5,128	809	387	0.75	3.77
Ireland	Male	2,356	537	257	1.09	5.45
	Female	2,407	428	205	0.85	4.25
Italy	Male	29,532	6888	3292	1.11	5.57
	Female	31,224	5686	2718	0.87	4.35
Latvia	Male	891	99	47	0.53	2.66
	Female	1,049	128	61	0.58	2.92
Lithuania	Male	1,296	216	103	0.80	3.98
	Female	1,521	307	147	0.96	4.82
Luxembourg	Male	302	52	25	0.82	4.12
	Female	301	49	23	0.78	3.89
Malta	Male	222	42	20	0.90	4.52
	Female	222	46	22	0.99	4.95
Netherlands	Male	8,534	2344	1120	1.31	6.56
	Female	8,664	1502	718	0.83	4.14
Poland	Male	18,377	1997	955	0.52	2.60
	Female	19,595	1982	947	0.48	2.42
Portugal	Male	4,877	1118	534	1.10	5.48
	Female	5,401	966	462	0.85	4.27
Romania	Male	9,511	717	343	0.36	1.80
	Female	9,982	707	338	0.34	1.69
Slovakia	Male	2,653	409	196	0.74	3.68
	Female	2,790	451	216	0.77	3.86
Slovenia	Male	1,027	272	130	1.27	6.33
	Female	1,042	265	127	1.22	6.08
Spain	Male	22,856	4060	1941	0.85	4.25
	Female	23,633	3751	1793	0.76	3.79
Sweden	Male	5,049	1153	551	1.09	5.46
	Female	5,038	826	395	0.78	3.92

Country	Gender	Population in 2018 (in 1000)	NHL incidence count for 2018	DLBCL incidence count for 2018	DLBCL incidence rate per 10k per yr in 2018	DLBCL prevalence per 10k in 2018
UK	Male	32,708	8746	4181	1.28	6.39
	Female	33,594	7193	3438	1.02	5.12
EU	Male	250,804	53,594	25618	1.02	5.11
	Female	262,351	43,797	20935	0.80	3.99
	Total	513,155	97,391	46553	0.91	4.54

DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin's lymphoma; yr = year

Note: European male and female population estimates for 2018 were obtained from Eurostat.

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 authorised products in the EU for the treatment of DLBCL:

- Rituximab (Mabthera) is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy;
- Pixantrone (Pixuvri) is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). Some chemotherapy agents are approved nationally in several EU countries under different trade names for the treatment of certain cancer types;
- Axicabtagene ciloleucel (Yescarta) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy;
- Tisagenlecleucel (Kymriah) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Several medicinal products are authorised and used for the treatment of Non-Hodgkin lymphomas. These include cyclophosphamide, doxorubicine, bendamustine, bleomycin, vincristine, vindesine, etoposide, iphosphamide, chlorabucil, lomustine, prednisone, and prednisolone, docetaxel, mitoxantrone, methotrexate, epirubicin, dexamethasone, cytarabine.

There is an ESMO treatment guideline on DLBCL ([Tilly et al, Ann Oncol \(2015\) 26 \(suppl 5\): v116-v125](#)) outlining the best standard of care of patients affected by the condition. The treatment guidelines are not updated to reflect currently authorised treatment options, i.e. CAR-T cell products tisagenlecleucel and axicabtagene ciloleucel.

Significant benefit

EMA protocol assistance on clinical development was requested prior to marketing authorisation, but no question with respect to the demonstration of significant benefit for the maintenance of the orphan status to be assessed by the COMP had been included by the sponsor. Significant benefit needs to be

demonstrated in adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. The current ESMO guideline does not indicate a preferred chemotherapy for these patients.

The results of clinical study GO29365 were submitted to demonstrate significant benefit. The same data were assessed by the CHMP for the establishment of benefit risk (please be referred to the European Public Assessment Report of Polivy). The pivotal study GO29365 is a Phase Ib/II, multicenter, open-label, multi-arm study (only the randomised arms C and D are relevant for this application) of polatuzumab vedotin in combination with bendamustine plus rituximab in patients with relapsed/refractory DLBCL. The median number of prior therapies of enrolled patients was 2 (range: 1-7), with 29% (n = 23) receiving one prior therapy, 25% (n = 20) receiving 2 prior therapies, and 46% (n = 37) receiving 3 or more prior therapies. On the basis of this trial, Polivy received conditional marketing authorisation in adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant. The COMP acknowledged that the indication for Polivy includes patients in 2nd line of treatment for which no approved treatment exists.

Furthermore, matching-adjusted indirect comparisons (MAIC) (Signorovitch et al. 2012) were provided to argue improved efficacy over therapeutic regimens Yescarta, Kymriah, and Pixantrone in third and late line DLBCL therapy. Moreover, improved safety was claimed highlighting specific adverse events that are associated with Yescarta and Kymriah. Finally, major contribution to patient care over Yescarta and Kymriah was argued on the basis that Polivy could be readily available without the need to wait for patient-specific manufacturing of the current CAR-T cell therapeutics.

The COMP noted the arguments on improved efficacy, improved safety and major contribution to patient care in third and late line DLBCL therapy. However, the COMP concluded that Polivy is of significant benefit because it is the first medicinal product with a specific indication in second line of treatment of diffuse large B-cell lymphoma. This is considered to be a clinically relevant advantage for patients affected by diffuse large B-cell lymphoma who are relapsed/refractory and are not candidates for haematopoietic stem cell transplant.

4. COMP position adopted on 5 December 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 treatment of diffuse large B-cell lymphoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 4.5 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 with 5-year survival rates reported as low as approximately 25% for high risk patients. The disease is curable in 60% of the patients;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, Polivy is of significant benefit to patients affected by diffuse large B-cell lymphoma who are relapsed/refractory and are not candidates for haematopoietic stem cell transplant. A phase Ib/II, multicenter, open-label, randomised study of Polivy in combination with bendamustine and rituximab demonstrated a significant increase in responses, supported by an improvement in progression free survival, when compared to bendamustine and rituximab therapy in adult patients with relapsed/refractory diffuse large B-cell lymphoma. Polivy is the first medicinal product with a specific indication in second line diffuse large B-cell lymphoma. The COMP considered that this demonstrates 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 Polivy, polatuzumab vedotin, EU/3/18/2013 for treatment of diffuse large B-cell lymphoma is not removed from the Community Register of Orphan Medicinal Products.