19 December 2017
EMA/977/2018
Orphan Maintenance Assessment Report

Orphan Maintenance Assessment Report

Adcetris (brentuximab vedotin)
Treatment of cutaneous T-cell lymphoma
EU/3/11/939 (EMA/OD/100/11)
Sponsor: Takeda Pharma A/S

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	Brentuximab vedotin
International Non-Proprietary Name	Brentuximab vedotin
Orphan indication	Treatment of cutaneous T-cell lymphoma
Pharmaceutical form	Powder for concentrate for solution for infusion
Route of administration	Intravenous
Pharmaco-therapeutic group (ATC Code)	L01XC12
Sponsor's details:	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup Denmark
Orphan medicinal product designation procedural history	
Sponsor/applicant	Takeda Pharma A/S
COMP opinion date	9 November 2011
EC decision date	11 January 2012
EC registration number	EU/3/11/939
Post-designation procedural history	
Transfer of sponsorship	Transfer from Takeda Global Research and Development Centre (Europe) Ltd to Takeda Pharma A/S – EC decision of 21 October 2013
Marketing authorisation extension of indication procedural history	
Rapporteur / co-Rapporteur	P. van Hennik / J. Mueller-Berghaus
Applicant	Takeda Pharma A/S
Application submission date	4 April 2017
Procedure start date	22 April 2017
Procedure number	EMEA/H/C/002455/II/0048
Invented name	Brentuximab vedotin
Therapeutic indication	Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy" Further information on Adcetris can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	9 November 2017
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	D. O'Connor / B. Bloechl-Daum / K. Kopečková
Expert	No experts were appointed by the COMP for this application
Sponsor's report submission date	5 May 2017
COMP discussion and adoption of list of questions	15 June 2017
COMP opinion date	7 December 2017

2. Grounds for the COMP opinion (at the designation stage)

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

- cutaneous T-cell lymphoma (hereinafter referred to as "the condition") was estimated to be affecting 2.2 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating due to the consequences of its clinical presentation, including cutaneous tumours, ulcerations, and erythroderma. The condition is life threatening in the most aggressive forms and also due to the risk of further malignant transformation;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that brentuximab vedotin may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the new mechanism of action which will improve the treatment options of patients with cutaneous T-cell lymphoma. This is supported by preclinical and clinical data.

3. Review of criteria for orphan designation at the time of extension of indication

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

C**ondition**

The applicant submitted this variation in order to extend the already existing indication.

Current indications:

- ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem cell transplant (ASCT) or
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

- - ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT .
- - ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Final proposed extension indication:

"ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy"

The COMP has considered several times that CTCL is a distinct medical entity. Cutaneous T-cell lymphoma refers to a heterogeneous group of primary cutaneous lymphomas, the most common type

of which is mycosis fungoides. The WHO-EORTC classification of 2005 (Willemze May 15, 2005; Blood: 105; 10) describes two groups, cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs) as forming the primary cutaneous lymphoma group. In the classification of tumours of haematopoietic and lymphoid tissues (Swerdlow 2016, Blood 127:20), the distinct types of primary cutaneous lymphomas are described separately with different codes, under the category of Mature T-cell and NK-cell neoplasms. In the 2013 ESMO treatment guidelines for primary cutaneous lymphomas, the WHO-EORTC classification is followed and the group of CTCL is presented as a separate entity (Willemze et al, Oncol 2013; 24 (Suppl 6): vi149-vi154).

The proposed therapeutic indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy" falls entirely within the scope of the designated orphan indication which is designated in broader terms as "treatment of cutaneous T-cell lymphoma".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat, prevent or diagnose the condition has been justified. Please refer to the EPAR of Adcetris.

Chronically debilitating and/or life-threatening nature

The applicant asserted that no change has been reported in the chronically debilitating or life-threatening nature of the condition since the orphan designation was granted on 11th January 2012. The condition is chronically debilitating due to manifestations such as cutaneous tumours, ulcerations, and erythroderma. The condition is life threatening in the most aggressive forms, also due to the risk of further malignant transformation.

Number of people affected or at risk

A point prevalence estimate was calculated from incidence, multiplied by the duration of the condition:

- The duration of the condition was conservatively considered to be approximately 20 years, on the basis of the median survival estimated to be 18.3 years among mycosis fungoides (MF) and Sézary syndrome (SS) cases, which represent the most common CTCL types.
- Data from all member states were considered for the purpose of identifying the incidence. The highest reported figure was approximately 0.1 per 10,000 incidence. This refers to an approximation of a reported rate of 0.084 for Germany, which was in turn calculated on the basis of German registry RKI data (for T-cell lymphoma) and SEER registry data (for a ratio referring to CTCL)

Based on these two figures, 20 years duration and 0.1 per 10,000 incidence, the COMP considered that the prevalence would be approximately 2 per 10,000 people at the time of review.

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 the 2013 ESMO clinical practice guidelines (Willemza et al, Annals of Oncology 24 (Supplement 6): vi149–vi154, 2013), the choice of treatment varies greatly, depending on the type of primary cutaneous lymphoma and the stage of disease. The two most common types are discussed below from these guidelines:

- With regards to Mycosis fungoides, patients with only patches and/or plaques covering <10% (stage IA) or ≥10% of the skin surface (stage IB) should be treated with skin-directed therapies, including topical steroids, psoralens + ultraviolet A (PUVA), narrow-band ultraviolet B (UVB) and topical cytostatic agents, such as mechlorethamine or carmustine (BCNU). For patients with more extensive infiltrated plaques and tumours or patients refractory to skin-directed therapies, a combination of PUVA and interferon alpha or PUVA and retinoids (including bexarotene), a combination of interferon alpha and retinoids or total skin electron beam irradiation can be considered. In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered (ESMO guidelines, Ann Oncol 2013; 24 (Suppl 6): vi149-vi154).
- For Sezary syndrome, systemic treatment is required. Skin-directed therapies like PUVA or potent topical steroids may be used as adjuvant therapy. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities such as interferon alpha, retinoids, total skin electron beam and PUVA, has been suggested as the treatment of choice in SS and erythrodermic MF (ESMO guidelines Ann Oncol 2013; 24 (Suppl 6): vi149-vi154).

Several products are authorised in the EU for the condition, either for CTCL specifically or for broader indications. The applicant has identified bexarotene, chlormethine, bleomycin, chlorambucil, cyclophosphamide, dexamethasone, doxorubicin, methotrexate, lomustine, mitoxantrone, interferon alpha, vinblastine and, vincristine. In addition to this list the COMP has also previously considered fluocinonide, betamethasone, clobetasol, carmustine, mechlorethamine, methylprednisolone, and triamcinolone to be authorised for the condition.

Significant benefit

The MA is mainly supported by the phase 3 study ALCANZA. ALCANZA was an open-label, randomised, multicentre study of brentuximab vedotin versus conventional therapy for previously treated patients with CD30-positive cutaneous T-cell lymphoma. Adult patients (aged ≥18 years) with CD30-positive mycosis fungoides who had received at least one previous systemic therapy, or adult patients with CD30-positive pcALCL who had received at least one previous systemic therapy or radiotherapy were enrolled.

Patients received either intravenous brentuximab vedotin 1.8 mg/kg once every 3 weeks, for up to 16 3-week cycles; or physician's choice of oral methotrexate 5–50 mg once per week, for up to 48 weeks, or oral bexarotene 300 mg/m2 once per day, for up to 48 weeks, until disease progression or unacceptable toxicity.

The primary endpoint was the proportion of patients achieving an objective global response lasting (from first to last response) at least 4 months, assessed by an independent review facility. Key secondary endpoints were proportion of patients achieving a complete response, progression-free

survival, and symptom burden measured by the symptom domain of health-related quality of life measure. The main results as shown in the table 1 below:

Table 1.

Endpoint	**BrentuximabVedotin N=64**	**Methotrexate or Bexarotene N=64**	**Difference Between Arms (95% CI)**	**Statistical Significance**
Primary Endpoint				
Number (%) achieving ORR4 per IRF	36 (56.3)	8 (12.5)	43.8 (29.1,58.4)	p<0.001
Key Secondary Endpoints				
Number (%) achieving CR per IRF	10 (15.6)	1 (1.6)	14.1 (-4.0,31.5)	Adj. p=0.0046
Median (months) PFS per IRF	16.7	3.5		Adj. p<0.0001 HR=0.270 (95% CI: 0.169, 0.430)
Skindex-29 symptom domain, mean maximum reduction (points)	-27.96	-8.62	-18.9 (-26.6,-11.2)	Adj. p<0.0001

ORR4 - Objective Response Lasting ≥4 months per Independent Review Facility
CR per IRF - Complete Response per Independent Review Facility
PFS per IRF - Progression-Free Survival per Independent Review Facility

The COMP considered the controls (physician's choice) in the study to be reflecting the standard of care and accepted the improved efficacy versus Methotrexate and Bexarotene as confirmation of significant benefit over those two authorised products. The COMP further discussed significant benefit versus interferon-A. As regards the justification of significant benefit versus interferon, the sponsor elaborated on the population included, and efficacy of the ALCANZA study, and proceeded with an indirect comparison versus published bibliography studies for IFN-α in CTCL and the SmPC of Roferon-a (interferon-α).

There were two comparisons put forward versus interferon alpha: a) a comparison of the ORR rate from Alcanza versus the ORR rate from the Roferon-A "summary of product characteristics" which numerically supports a clinically relevant advantage and b) a comparison of the median time to next treatment analysis (TNTT) versus an analysis of Hughes and co-workers (Blood 2015;125(1):71-81.) This was a retrospective analysis of a cutaneous lymphoma database with 198 MF/SS patients undergoing systemic therapies. The primary end point was time to next treatment (TTNT) and this was reported to be approximately 9 months (8.7 months). With reference to that analysis, the applicant reported that brentuximab vedotin had a longer TTNT based on the ALCANZA results (14.3 months).

Table 2. Efficacy in ALCANZA study versus IFNα information (source: sponsor response)

Therapy	ORR	ORR4 per IRF (95% CI)	Median TNTT (months)	TTNT 95% CI (months)
ALCANZA study(a)				
Brentuximab vedotin	67.2%	56.3% (44.1, 68.4)	14.3	12.5, 20.4
Physician's choice	20.3%	12.5% (4.4, 20.6)	5.5	3.6, 7.2
Bexarotene	26.3%	15.8% (4.2, 27.4)	6.6	4.2, 8.3
Methotrexate	11.5%	7.7% (0.9, 25.1)	4.6	2.4, 6.4
IFN-α	58%(b)	NA	8.7(c)	6.0-18.0

NA=not available
[a] ALCANZA clinical study report, 2017 Appendix C
[b] Roferon-A SmPC
[c] Hughes et al, Blood 2015;125(1):71-81

With regards to the effects of Brentuximab in patients of the ALCANZA trial who were previously treated patients with interferon-a, the sponsor clarified that 26 patients in the Adcetris arm and 28 patients in the phycisian's choice arm (bexarotene or methotrexate) had previously received interferon. In those patients ORR was reported to be 54% and 7% respectively. The COMP considered that such observations are relevant for the confirmation of a clinically relevant advantage in patients that had received interferon-α and subsequently progressed.

It was therefore concluded that the available clinical data support durable clinical responses compared to standard of care, in patients who had previously received at least one prior therapy, including patients who had received interferon-α. This was considered a clinically relevant advantage.

4. COMP position adopted on 7 December 2017

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 approximately 2 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 consequences of its clinical presentation, including cutaneous tumours, ulcerations, and erythroderma. The condition is life threatening in the most aggressive forms and also due to the risk of further malignant transformation;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Adcetris may be of potential significant benefit to those affected by the orphan condition still holds. The available clinical data support durable clinical responses compared to standard of care, in patients who had previously received at least one prior therapy, including patients who had received interferon-α. The committee 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 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 Adcetris, brentuximab vedotin, EU/3/11/939 for treatment of cutaneous T-cell lymphoma is not removed from the Community Register of Orphan Medicinal Products.