6 February 2019
EMA/115413/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Adcetris (monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E)
Treatment of Hodgkin lymphoma
EU/3/08/596 (EMEA/OD/073/08)
Sponsor: Takeda Pharma A/S

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

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1. Product and administrative information

Product	
Active substance	Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E
International Non-Proprietary Name	Brentuximab vedotin
Orphan indication	Treatment of Hodgkin 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	Seattle Genetics UK Limited
COMP opinion date	8 October 2008
EC decision date	15 January 2009
EC registration number	EU/3/08/596
Post-designation procedural history	
Transfer of sponsorship	Transfer from Seattle Genetics UK Limited to Takeda Global Research and Development Centre (Europe) Ltd – EC decision of 28 September 2010
Transfer of sponsorship	Transfer from Takeda Global Research and Development Centre (Europe) Ltd to Takeda Pharma A/S – EC decision of 21 October 2013
Type II variation procedural history	
Rapporteur / co-Rapporteur	P.B. van Hennik, J. Mueller-Berghaus
Applicant	Takeda Pharma A/S
Application submission date	28 November 2017
Procedure start date	3 March 2018
Procedure number	EMA/H/C/002455/II/0055
Invented name	Adcetris
Therapeutic indication	Adcetris is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).
CHMP opinion date	13 December 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	B. Dembowska-Baginska, K. Penttila
Sponsor's report submission date	25 April 2018
COMP discussion and adoption of list of questions	22-24 May 2018
Oral explanation	22 January 2019
COMP opinion date	24 January 2019

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2008 was based on the following grounds:

- Hodgkin lymphoma (hereinafter referred to as "the condition") was estimated to be affecting approximately 1 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to the poor long-term prognosis in patients that progress during or shortly after initial chemotherapy;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E may be of significant benefit to those affected by the condition.

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

Hodgkin lymphoma (HL), formerly called Hodgkin's disease, arises from germinal center or post-germinal center B cells, and is characterised by a minority of neoplastic cells (Reed-Sternberg cells and their variants) in an inflammatory background. There are two groups of HL, namely classical, and nodular lymphocyte predominant HL. Although the classification of Hodgkin lymphomas (HLs) has not changed, the 2016 revision of the World Health Organization classification of lymphoid neoplasms will include updates concerning nodular lymphocyte–predominant HL (NLPHL) (Swerdlow, Blood 2016 127:2375-2390). Most patients present with a painless localized peripheral lymphadenopathy, typically in the cervical area, while systemic manifestations such as B-symptomatology (fever, drenching night sweats, weight loss) and pruritus may also be present. Mediastinal masses are also frequent and are sometimes discovered after routine chest x-ray. The proposed condition continues to be a distinct medical entity and suitable orphan condition.

The proposed therapeutic indication is "ADCETRIS is indicated for the frontline treatment of adult patients with CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)" falls within the scope of the designated orphan indication "treatment of Hodgkin Lymphoma".

Intention to diagnose, prevent or treat

Based on the positive CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any change in the seriousness of the condition since the designation. Mortality from HL has been progressively decreasing with recent 5-year survival rates of more than 80%, (Gobbi et al. Crit Rev Oncol Hematol. 2013 Feb;85(2):216-37 Eichenauer et al, Ann Oncol

(2014) 25 (suppl 3): iii70-iii75) but the condition is still chronically debilitating and life threatening in particular in patients with refractory or relapsed disease. The likelihood of achieving a complete response to treatment and a sustained remission diminishes with second and subsequent relapses, while outcomes following treatment for refractory HL are even less favourable than following relapses. In patients who are able to undergo autologous HCT, long-term survival can approach 50% percent (Moskowitz, Br J Haematol. 2004;124(5):645).

Number of people affected or at risk

The sponsor proposes 5-, 10- and 20-year prevalence estimates to be 1.16, 2.19, and 3.92 per 10,000, respectively. This was calculated indirectly based on the following methodology:

- Incidence was first calculated for each country from national sources as far as possible. Sources for incidence included: the National Cancer Registry of Germany, the National Cancer Registry of Poland, National Cancer Registry of Netherlands, the Office of National Statistics of UK estimates respectively, EUREG, IARC, NORDCAN. For EU28 countries with no specific incidence data, extrapolations were made from the countries with available data.
- With regards to survival, 2000-2014 data extracted from the SEER database were used. It was noted that for some lower income countries adjustments were made by comparing the mortality-to-incidence ratios as reported by the International Agency for Research on Cancer (IARC, 2012).

Based on the assumed duration of up to approximately 20 years (Bessell, Bouliotis et al. British Journal of Cancer (2012) 107, 531–5362012) a 4 per 10,000 conclusion on prevalence was considered acceptable for this extension procedure.

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 recommended therapeutic algorithm for newly diagnosed Hodgkin's lymphoma revolves around chemotherapy and radiotherapy(Eichenauer et al. Annals of Oncology 2018, 29 S4 iv19–iv29).

The regimen ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), alone or in combination with BEACOPP is recommended for limited and intermediate stages, followed by involved field radiotherapy. Advanced -stage HL is usually treated with chemotherapy alone, and patients younger than 60 years are treated with either ABVD (six cycles) or BEACOPP escalated (four to six cycles), optionally followed by localised radiotherapy (Eichenauer et al. Annals of Oncology 2018, 29 S4 iv19–iv29). ABVD-based chemotherapy is discussed as the standard of care for older HL patients who are fit enough for multi-agent chemotherapy.

In its maintenance report, the sponsor provided a list of authorised products with indications covering Hodgkin’s Lymphoma. From those indicated for first line treatment, most are included in the chemotherapy regimens ABVD and BEACOPP. The relevance of the comparisons versus those two standards of care for the purpose of justifying significant benefit was therefore endorsed.

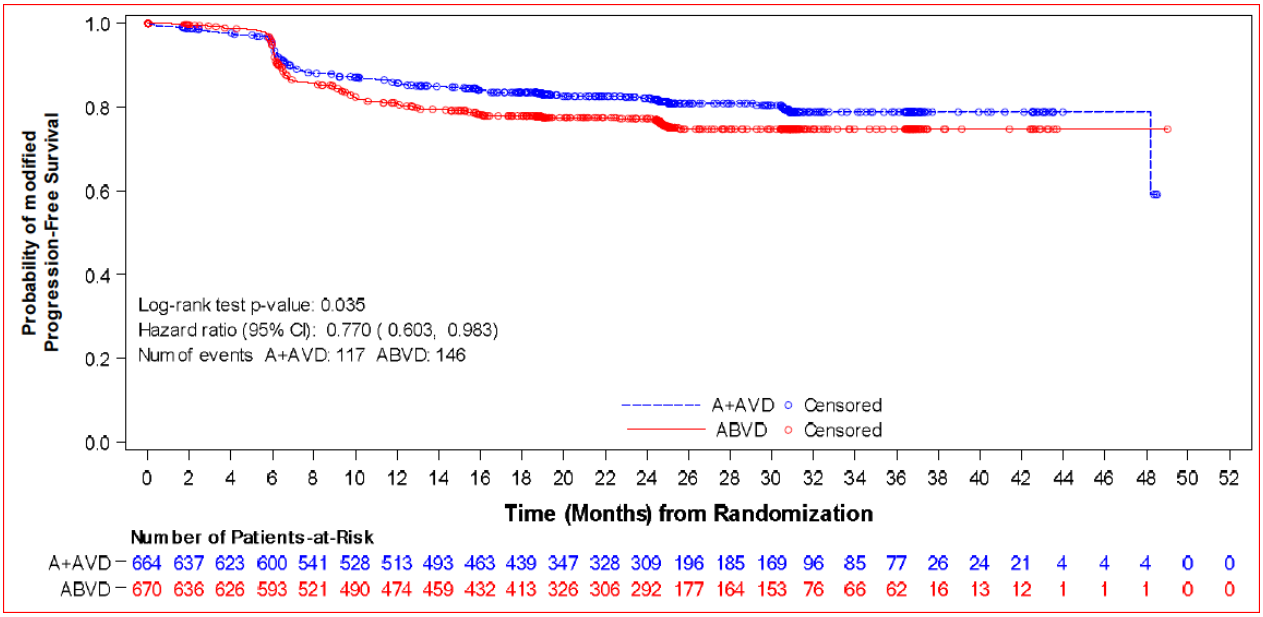
Significant benefit

The applicant provided a discussion in settings that are not directly relevant for the extension (such as ASCT and R/R settings), and a short discussion in front line disease based on the main study (ECHELON-1) that supported the marketing authorisation.

The ECHELON-1 was the pivotal study to support the efficacy of brentuximab vedotin in frontline treatment of adult patients with CD30+ advanced Hodgkin Lymphoma (HL) in combination with chemotherapy. The results showed superior efficacy for the A+AVD versus ABVD and the primary endpoint was mPFS, assessed in the ITT population using the revised response criteria for malignant lymphoma per IRF. The significant benefit versus ABVD was therefore justified.

In particular, as of the 20 April 2017 data cut-off date for the primary analysis of the primary endpoint, median mPFS was not reached in either treatment arm. At this time, 117 mPFS events had been observed in the A+AVD arm and 146 mPFS events had been observed in the ABVD arm (Figure 1). A+AVD was associated with a 23.0% reduction in the risk of an mPFS event versus ABVD (HR=0.770; 95% CI, 0.603-0.983). This improvement was statistically significant (P=0.035). The proportion of patients free from an mPFS event at 2 years after randomization was 82.1% in the A+AVD arm versus 77.2% in the ABVD arm (95% CI, 78.8-85.0% versus 73.7-80.4%).

Figure 1. KM plot of mPFS



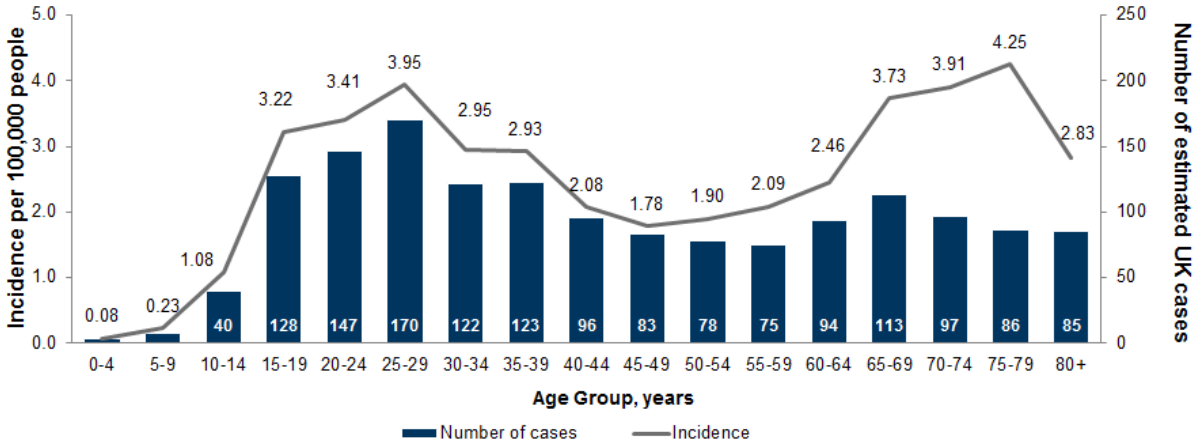
With regards to the significant benefit versus BEACOPP, the applicant embarked in an effort to produce comparisons of BEACOPP versus ABVD to argue comparable efficacy, and then to proceed with an argument by "extension" of the improved efficacy of A+AVD versus ABVD to also argue improved efficacy of A+AVD versus BEACOPP. However, the sponsor also acknowledged that "Literature is inconclusive on the superiority of either regimen" [referring to ABVD, BEACOPP] which makes it difficult to perform such an extrapolation. The COMP therefore did not consider this argument.

Two other arguments put forwards were improved safety versus BEACOPP, focusing on its use in young and fit patients, as well as a major contribution to patient care. Of those arguments, the claim of a major contribution to patient care was not considered plausible, as patients are already engaged in complex chemotherapy regimens, and there was an absence of PRO data confirming improvements linked to the new posology.

On the other hand the available European ESMO guidelines, point out that the BEACOPP regimen is not recommended in patients with an age of more than 60 years old. This point was further explored with the applicant, given that the authorised indication of Adcetris does not have an age restriction. The sponsor was asked in particular to document the issues necessitating a restriction of BEACOPP use in the older population.

In response, the sponsor firstly noted that the epidemiology of the disease has two well known peaks, with the second affecting patients after the 6th decade of life.

Figure 2.



HMRN Researchers. HMRN incidence – Classical Hodgkin lymphoma. 2018 Available at: https://www.hmrn.org/statistics/incidence. Accessed Apr 24, 2018; 2. Skoetz N, et al. *Cochrane Database Syst Rev*. 2017;5:CD007941; 3. Gatta G, et al. *Eur J Cancer*. 2011;47(17):2493-511.

The applicant further elaborated on the treatment related mortality as described in the literature. In a 2009 publication for the HD9 trial from the German Hodgkin Study Group (Engert et al, Journal of Clinical Oncology 27(27): 4548-4554), the respective treatment related mortality led to the change in upper age limit for future use in GHSG trials to 60 years old. The increased treatment related mortality in patients over 40 and 50 years was also documents in a retrospective analysis of the HD9, HD12 and HD15 studies (Wongso D J Clin Oncol 31:2819-2824, 2013).

In contrast, the newly approved indication for Adcetris has no age-restriction. With reference to the CHMP assessment, elderly patients with stage IV HL have a trend towards a slightly favourable mPFS treated with A+AVD versus ABVD [n=118 age ≥60] (mPFS per IRF: HR = 0.804 (95% CI: 0.42 to 1.53), p = 0.506) and for age ≥65 [n=78] HR = 0.777 (95% CI: 0.36 to 1.67), p = 0.515). The subsets of elderly patients with Stage IV HL (n=118 patients aged ≥60; n=78 patients aged ≥65) is relatively small. Even so, among elderly patients with Stage IV HL, favourable trends for mPFS and OS were observed.

The COMP accepted based on these justifications that the A+AVD combination would be applicable in a broader population compared to (esc) BEACOPP.

4. COMP position adopted on 24 January 2019

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 Hodgkin lymphoma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be approximately 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 the poor long-term prognosis in patients that progress during or shortly after initial chemotherapy;
- 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 applicant has provided clinical data in the first line treatment of advanced Hodgkin lymphoma, that show improved progression free survival when the product is added on to AVD versus that obtained with ABVD, the latter being one of the two standard of care regimens;
- the committee also considered that (escalated) BEACOPP, the other standard of care, is used in younger patients, due to the increasing treatment related mortality with age and as attested by the respective European practice guidelines. In contrast, there is no age restriction with respect to the use of Adcetris. 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 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, monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E, brentuximab vedotin, EU/3/08/596 for treatment of Hodgkin lymphoma is not removed from the Community Register of Orphan Medicinal Products.