12 October 2023
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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

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	
Designated active substance(s)	Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E
Other name(s)	Adcetris, Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E
International Non-Proprietary Name	Brentuximab vedotin
Tradename	Adcetris
Orphan condition	Treatment of Hodgkin lymphoma
Sponsor's details:	Takeda Pharma A/S Delta Park 45 2665 Vallensbaek Strand Hovedstaden Denmark
Orphan medicinal product designation procedural history	
Sponsor/applicant	Seattle Genetics UK Limited
COMP opinion	8 October 2008
EC decision	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 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	Johann Lodewijk Hillege / Jan Mueller-Berghaus
Applicant	Takeda Pharma A/S
Application submission	8 March 2023
Procedure start	25 March 2023
Procedure number	EMA/H/C/002455/II/0107
Invented name	Adcetris
Proposed therapeutic indication	Treatment of adult patients with previously untreated CD30+ Stage **III or** IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD). Further information on Adcetris can be found in the European public assessment report (EPAR) on the Agency's website: http://www.ema.europa.eu/en/medicines/human/EPAR/Adcetris
CHMP opinion	14 September 2023

COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Elisabeth Johanne Rook / Frauke Naumann-Winter
Sponsor's report submission	6 April 2023
COMP discussion	11-13 July 2023
COMP opinion (adoption via written procedure)	19 September 2023

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2008 designation 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.

2.2. Amendment of an existing orphan medicinal product designation

The COMP opinion that was the basis for the amendment of the orphan medicinal product designation in 2023 was based on the following grounds:

- 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.

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. Young adults aged 20–40 years are most often affected (Annals of Oncology 29 (Supplement 4): iv19–iv29, 201).

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 Ann Arbor staging classification for Hodgkin lymphoma defines stage I as involvement of a single nodal region or organ, stage II as involvement of two or more regions on the same side of the diaphragm, stage III as involvement of nodal regions on both sides of the diaphragm, and stage IV as diffuse extralymphatic involvement. The presence of high fevers, night sweats, or significant weight loss designates any given stage as "B" (e.g., IIB).

The approved extension of the therapeutic indication is "*ADCETRIS is indicated for the frontline treatment of adult patients with CD30+* ***Stage III*** *and 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

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any change in the seriousness of the condition since the designation, nor the initial authorisation, which is supported.

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. For stage III, the 5 years survival is about 80%, whereas this is 65% for Stage IV.

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).

The COMP considers the condition chronically debilitating and life threatening, particularly in advanced disease stage.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 4.3 per 10,000 persons.

This estimate is slightly higher than the previously accepted prevalence estimate of 4 per 10,000 persons and is based on data for Hodgkin lymphoma (HL) from 31 European countries, i.e. the EU27 member states, plus Iceland, Liechtenstein, Norway and United Kingdom. For this procedure only the data for overall HL was considered. The sponsor had also submitted data on the prevalence for classical HL (cHL) and stage III and IV cHL.

The final prevalence estimates were 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 Bulgaria, National Cancer Registry of Netherlands, the Office of National Statistics of UK estimates, , Public Health France, Belgian Cancer Registry, Croatian National Cancer Registry, Czech National Cancer Registry, National Cancer Registry of Ireland, Cancer Registry of Slovenia, National Oncology Registry of Portugal, IARC, NORDCAN. For countries with no specific incidence data, extrapolations were made from the countries with available data.
- With regards to disease duration/survival, data from the "*Surveillance, Epidemiology, and End Results database*", (SEER 1992-2019 and SEER 2000-2019) were used. From both the SEER incidence and limited duration prevalence, the mean disease duration was calculated at the 5-, 10-, and 20- year time frame (under the assumptions of stable incidence and duration of the condition, the functional relationship between point prevalence (P), incidence (I) and mean duration (D) is commonly expressed as P = I x D).

To estimate the prevalent population for HL, the applicant multiplied the country-specific incidence estimates with 5-, 10-, and 20-year mean duration (D) to estimate the 5-, 10-, and 20-year country-specific prevalence respectively. The sponsor's proposed prevalence estimate of 4.3 per 10,000 persons represents the 20-year prevalence for HL. This was also accepted by the COMP during the initial orphan designation review based on the assumed duration of up to approximately 20 years (Bessell, Bouliotis et al. British Journal of Cancer (2012) 107, 531–5362012).

The COMP pointed out that the proposed 20-year prevalence estimate of 4.3 per 10,000 persons still includes a non-EU/EEA country. The sponsor has also provided an analysis without the data from this non-EU/EEA country which resulted in a slightly lower 20-year prevalence estimate of 4.2 per 10,000 persons.

The committee accepted a 20-year prevalence estimate of 4.2 per 10,000 persons.

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 and is reflected in detail in the latest ESMO treatment guideline from 2018 (Eichenauer et al. Annals of Oncology 2018, 29 S4 iv19–iv29). In this report, only those chemotherapies/regimens will be discussed which constitute the current standard of care in the applied for target population of Adcetris.

In the frontline setting, combination chemotherapy (ChT) regimens with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and/or BEACOPP (bleomycin/ etoposide/ doxorubicin/ cyclophosphamide/ vincristine/ procarbazine/ prednisone) or escalated BEACOPP are regarded as standard of care regimens in the EU in adult patients with advanced-stage classical HL. However, the BEACOPP regimen should not be given to the patients > 60 years. Therefore, ABVD-based ChT represents the standard of care for older HL patients who are fit enough for multi-agent ChT.

Significant benefit

For demonstrating significant benefit versus ABVD, reference is made to the pivotal trial ECHELON-1.

ECHELON-1 (Study C25003) is a randomized, open-label, phase 3 study which compared the efficacy and safety between the standard of care ChT regimen ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine; n=670) with the modified ChT regimen in which bleomycin was substituted with Adcetris (A+AVD; n=664) in patients with Stage III or Stage IV classical HL. The primary endpoint was modified progression-free survival (mPFS) by independent review. Overall survival (OS) was the key secondary endpoint.

In 2019, Adcetris in combination with AVD was authorised for an extension of indication to first line treatment in Stage IV Hodgkin lymphoma (HL). At that time, the Marketing Authorisation Holder did not apply for the Stage III HL indication as in this subset, there were uncertainties regarding the benefits in this subgroup. Based on the 2017 first interim analysis of the pivotal study, the OS HR was 1.216 (95% CI 0.563-2.630) in this subgroup, although there was a tendency for improved mPFS in this subgroup.

The CHMP agreed, in a Protocol Assistance, that the sponsor could resubmit data from the ECHELON study after longer term follow-up (5 years, when minimum event of 103 are achieved). The CHMP now approved the extension of indication to Stage III HL, based on the results from the second interim analysis in 2021 of the ECHELON-1 extension study.

The efficacy conclusions from the 2021 interim analysis are as follows:

Analyses by disease stage (III or IV) show a consistent strong PFS per investigator and OS result among patients with Stage IV cHL that has been maintained over a longer follow-up duration.

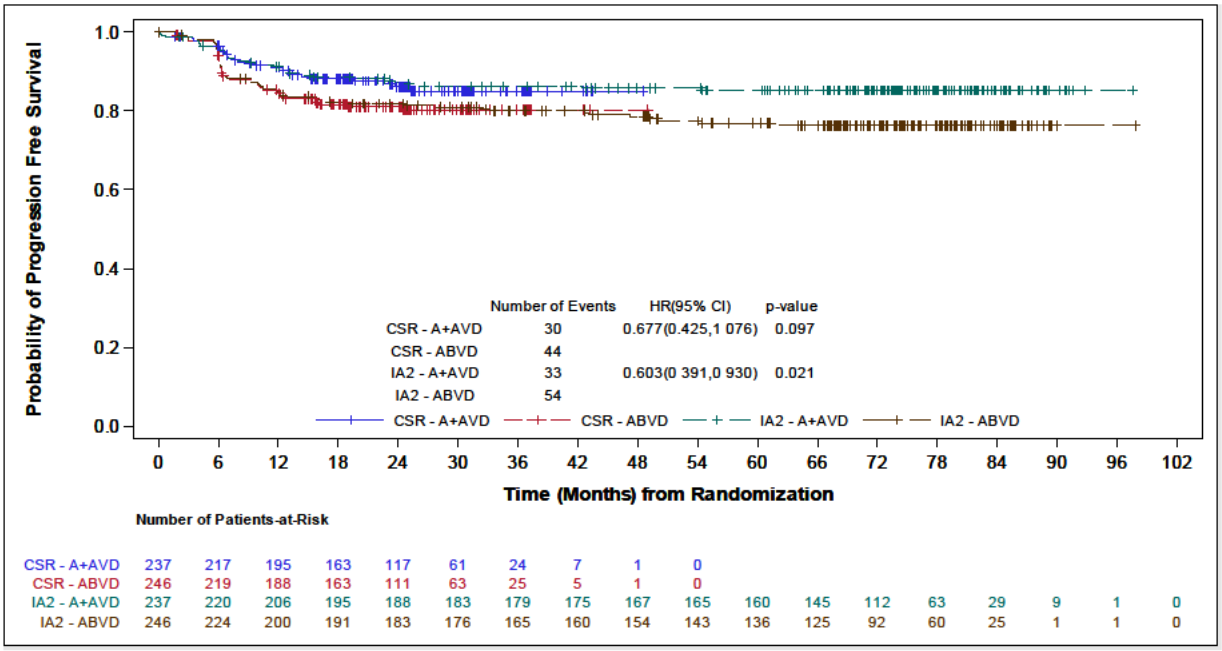
Among the 846 ITT population patients with Stage IV disease, the PFS per investigator HR as of the 2017 analysis was 0.705 (95% CI 0.530, 0.937; descriptive p=0.203). As of this analysis, PFS per investigator for patients with Stage IV disease now shows a comparable HR of 0.717 with the upper boundary of the 95% CI remaining below unity (95% CI 0.534-0.959, descriptive p-value=0.024).

Among the 483 ITT population patients with Stage III disease, the PFS per investigator HR as of the 2017 analysis was 0.766 (95% CI 0.507, 1.156; descriptive p=0.203). As of this analysis, PFS per investigator for patients with Stage III disease now shows an improved HR of 0.603 with the upper boundary of the 95% CI below unity (95% CI 0.391-0.937, descriptive p-value=0.021).

The absence of a PFS event in the ITT population was associated with higher quality of life at each posttreatment time point as per EORTC QLQ-C30 (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Core 30) global health status/QoL subscale scores.

In Figure 1 an overlay of the 2017 and 2021 Kaplan-Meier curves for PFS per investigator in ITT subset with Stage III HL is presented. As of the 2021 analysis, 14% of patients randomized to A+AVD and 22% of patients randomized to ABVD had experienced a PFS event, representing a 40% reduction in the risk of death or disease progression per investigator for patients randomized to A+AVD. The nominal P-value for this analysis was <0.05. Overall, additional observation has revealed clear separation of the PFS curves beginning soon after the in-treatment period and continuing to the point of data cutoff.

Figure 1. ECHELON-1: Progression-Free Survival per Investigator at Primary Analysis (CSR) versus Interim Analysis 2 (IA2) (ITT Subset with Stage III HL)



Source: Figure 99.2.9.1A, data cutoffs 20 April 2017 and 01 June 2021. Hazard ratio (A+AVD/ABVD) and 95% CI based on unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD arm. A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CSR, clinical study report 2017 primary endpoint analysis; IA2, interim analysis 2 long-term follow up 2021 analysis as of 103 deaths.

OS hazard ratios have improved in each disease stage subset over time. Patients with Stage IV cHL had an OS HR of 0.507 (95% CI 0.265-0.971) as of the 2017 first interim analysis; as of this analysis the OS HR is now 0.478 (95% CI 0.286-0.0.799).

Patients with Stage III cHL had an OS HR of 1.216 (95% CI 0.563-2.630), as of the 2017 first interim analysis, not excluding a detrimental treatment effect in this subgroup. Importantly, as of this analysis the OS HR now indicates a positive trend in treatment effect with a HR of 0.863 (95% CI 0.452-1.648), in the same direction as the ITT (intention-to-treat) analyses of the overall study population (Stage III plus Stage IV).

Overall, treatment with A+AVD provided a durable efficacy benefit in ITT population patients with treatment-naïve Stage III and IV cHL which is supported by the subgroup analyses of either disease stage subgroup, including patients with Stage III cHL.

There was a higher incidence of neuropathic events on the A+ AVD study arm as compared to the ABVD arm (67% vs 43%), of which 86% waned off at longer follow-up. On the other hand, the mortality rate was higher for the ABVD group. In conclusion, the COMP considered that Adcetris may be of potential significant benefit to those affected by the orphan condition. The sponsor has provided updated clinical data in the first line treatment of stage III and stage IV classical Hodgkin lymphoma, that show improved progression free survival when the product is added on to AVD versus that obtained with the ABVD standard of care chemotherapy regimen. The COMP considered that this constitutes a clinically relevant advantage.

With regards to the second standard of care treatment option the (escalated) BEACOPP chemotherapy regimen, the committee also considered that this is only recommended in younger patients, due to the increasing treatment related mortality with age and as laid down in European practice guidelines. In contrast, there is no age restriction with respect to the use of Adcetris. About 14% of the study population of the ECHELON study consisted of elderly, and also in this subgroup there was a tendency for improved mPFS response, without aberrant safety problems as compared to younger patients.

In conclusion, the sponsor has provided clinical data in the first line treatment of Stage III and Stage IV Hodgkin lymphoma, that show improved progression free survival and overall survival when the product is added to AVD (adriamycin, vinblastine, dacarbazine) versus that obtained with the standard of care regimen ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). The COMP considered that this constitutes a clinically relevant advantage.

4. COMP position adopted on 19 September 2023

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 Hodgkin lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.2 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 particularly in advanced disease stage;
- 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 Stage III and Stage IV Hodgkin lymphoma, that show improved progression free survival and overall survival when the product is added to AVD (adriamycin, vinblastine, dacarbazine) versus that obtained with the standard of care regimen ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). 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 for treatment of Hodgkin lymphoma (EU/3/08/596) is not removed from the Community Register of Orphan Medicinal Products.