12 May 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Adcetris (brentuximab vedotin)
Treatment of peripheral t-cell lymphoma
EU/3/08/595
Sponsor: Takeda Pharma A/S

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Active substances at the time of orphan designation	Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E
Other names	Anti-CD30-MMAE; Anti-CD30-monoclonal-antibody-cAC10-auristatin-E-conjugate; Auristatin-E-anti-CD30-monoclonal-antibody-cAC10-conjugate; cAC10-vcMMAE; MMAE-anti-CD30; SGN-35
International Non-Proprietary Name	Brentuximab vedotin
Tradename	Adcetris
Initial orphan condition	Treatment of anaplastic large cell lymphoma
Amended orphan condition (at time of review of criteria for orphan designation)	Treatment of peripheral t-cell lymphoma
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/3/08/595
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 30 September 2010
COMP opinion on review of orphan designation at the time of marketing authorisation	5 September 2012
Transfer of sponsorship	Transfer from Takeda Global Research and Development Centre (Europe) Ltd to Takeda Pharma A/S – EC decision of 23 October 2013
Change of designated condition COMP opinion date	18 July 2019
Change of designated condition EC decision date	23 August 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	P.B. van Hennik / J. Mueller-Berghaus
Applicant	Takeda Pharma A/S
Application submission date	19 June 2019
Procedure start date	20 July 2019
Procedure number	EMA/H/C/002455/II/0070
Invented name	Adcetris

Proposed therapeutic indication	Adcetris in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL). Further information on Adcetris can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris
CHMP opinion date	26 March 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E.J. Rook/ A. Magrelli
Sponsor's report submission date	22 August 2019
COMP discussion	8-10 October 2019
Adoption of list of questions	19 March 2020
Oral explanation	22 April 2020
COMP opinion date	23 April 2020

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 2009 designation was based on the following grounds:

- anaplastic large cell lymphoma (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.2 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to poor overall survival;
- 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 2019 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E / brentuximab vedotin was considered justified based on clinical responses with the product as a monotherapy in relapsed/refractory patients, as well as clinical studies in first line in combination with existing treatments resulting in improved survival;
- the condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses;

- the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E / brentuximab vedotin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing responses with the product as a monotherapy in relapsed/refractory patients, as well as clinical studies in first line in combination with existing treatments resulting in improved survival. The Committee considered that this constitutes a clinically relevant advantage.

2.3. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2012 was based on the following grounds:

- the sponsor has been granted two orphan designations for monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin as a medicinal product; firstly for the "treatment of Hodgkins' lymphoma" (EU/3/08/596) and secondly for the "treatment of anaplastic large cell lymphoma" (EU/3/08/595);
- the proposed therapeutic indication "treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1) following autologous stem cell transplant or 2) following at least two prior therapies when autologous stem cell transplantation is not a treatment option and treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)." falls entirely within the scope of the abovementioned orphan indications of the designated Orphan Medicinal Product;
- the prevalence of anaplastic large cell lymphoma (hereinafter referred to as "the condition") was estimated to be 0.2 in 10,000 and remains below 5 in 10,000 at the time of the review of the designation criteria;
- the condition is life-threatening with a 5-year survival of 29-44%;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin may be of potential significant benefit to those affected by the orphan condition still holds. Patients with refractory and relapsed anaplastic large cell lymphoma who no longer responded to any therapy showed prolonged survival time when treated with monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin.

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

It is to be noted that in August 21, 2019 a previous designation for the "treatment of anaplastic large cell lymphoma" has been amended to "treatment of peripheral T-cell lymphoma".

Peripheral T-cell lymphomas (PTCLs) are a collection of rare malignancies and a biologically heterogeneous group of lymphomas. Derived from mature T-cells and natural killer (NK) cells, there are many histological subtypes considered by the 2016 World Health Organization (WHO) classification (Swerdlow, Campo et al. Blood 2016 127:20: 2375–2390, Sandell RF, Boddicker RL, Feldman AL. *Curr Oncol Rep*. 2017;19(4):28). The European Society of Medical Oncology (ESMO) have issued clinical guidance for the diagnosis, treatment and follow up for 8 primary nodal and extra-nodal PTCL histologies (d'Amore et al. 2015 Ann Oncol 26:S5 v108-v115). The amended condition as designated encompasses nodal, extranodal, and leukemic/disseminated histological subtypes. Anaplastic large-cell lymphoma (ALCL), pertinent to this procedure, is a primary nodal subtype.

The therapeutic indication: "Adcetris in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)*"* falls entirely within the scope of the designated orphan condition "Treatment of peripheral T-cell lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility has been justified considering the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The COMP has considered that the condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive sub-types.

Number of people affected or at risk

The incidence and prevalence (5, 10, 20-year and lifetime prevalence) of PTCL for 2017 were estimated in 31 European countries: 27 EU member states, plus UK, Iceland, Liechtenstein and Norway. The sponsor has conducted a literature and registry review to identify incidence rates, and survival was calculated based on SEER (Surveillance, Epidemiology, and End Results) data.

When country specific studies were unavailable, results were extrapolated from studies based in comparable populations. The sponsor reports that there is substantial variation in the crude incidence of PTCL among the countries, which is reported up to the highest figure of approximately 1.11 per

100,000 population per year in Netherlands (with reference to National Cancer Registry of the Netherlands, INKR, 2017).

By assuming a median survival of approximately 9 years, the multiplication of yearly incidence rate times survival would yield up to approximately 0.999 or 1 per 10,000 in the NL. This mean survival estimate was indirectly derived from cutaneous lymphomas literature (Agar et al, 2010 J Clin Oncology 28(31): 4730-9) which was later on adjusted for PTCL using SEER data.

In previous orphan procedures PTCL was estimated to be affecting less than 1 in 10,000 persons in the European Union, which is in line with the highest estimation of the sponsor, assuming an incidence up to 0.111 per 10,000 (for NL) and an approximate duration of 9 years as described above. It was considered that this conclusion could serve as a proxy for all patients alive with a previous diagnosis of peripheral T-cell lymphoma.

The condition was therefore estimated to affect less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

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 sponsor has outlined the currently authorised products for the treatment of peripheral T-cell lymphoma and/or non-Hodgkin lymphoma. These include brentuximab vedotin (the same product was already authorised in relapsed or refractory systemic anaplastic large cell lymphoma at the time of this indication extension), rituximab, pixantrone, idelalisib, lomustine, bleomycin, betamethasone, cyclophosphamide, doxorubicin, dexamethasone, prednisolone, epirubicin, ifosfamide, triamcinolone, chlorambucil, bendamustine, mitoxantrone, procarzabine, IFN-α, vinblastine, vincristine, teniposide, nelarabin, etoposide, cytarabine, methotrexate .

The COMP noted the relevant ESMO guideline for PTCL covering the systemic subtypes of primary nodal and primary extranodal PTCL (F. d'Amore et al, Ann Oncol 2015, 26 S5:v108-v115.), according to which treatment options for first line PTCL revolve around schemes such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or for patients younger than 60 with addition of etoposide, CHOEP, followed by SCT (stem cell transplantation) for eligible patients. Whenever possible, inclusion in a clinical trial is recommended, including in the first line.

In particular, for nodal PTCL (PTCL-NOS, AITL,which includes sALCL ALK+ and sALCL ALK−), CHOP or variants of it has been the most commonly used regimen. In patients less than 60 years of age with ALCL ALK+ histology, CHOP with the addition of etoposide (CHOEP) has shown some outcome benefits in terms of event-free survival but not overall survival (OS). CHOEP was mostly feasible in younger patients (≤60 years), toxicity being a limiting factor in older patients.

Significant benefit

In evaluation of the significant benefit, the scope of the extension is first line and therefore all authorised products used in first line regimens will have to be taken into consideration. However, there is an issue with the articulation of the indications of the identified authorisations, in that they are vaguely worded and often refer to "NHL" indications in general. Therefore, it may be agreed that the

ESMO guidelines can provide pro tanto guidance with regards to which products can be considered as satisfactory for the purpose of establishing significant benefit.

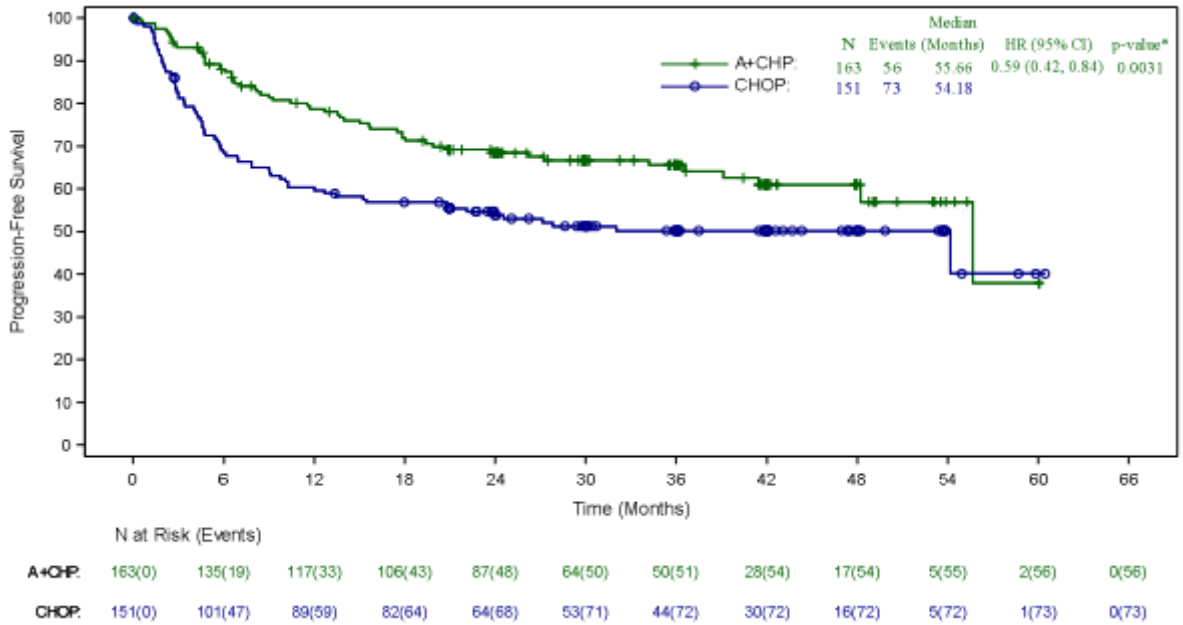
The relevant comparators can be the identified by taking into consideration that most patients in the ECHELON study (70%) were ALCL patients. Therefore, based on the ESMO recommendations for nodal PTCL, a comparison versus CHOP and CHOEP was considered relevant for this discussion.

Significant benefit versus CHOP

A significant benefit was argued by the sponsor based on data from the ECHELON-2 study, showing a statistically significant improvement in PFS and OS across the population of that study, composed of patients with CD30+ PTCL who were treatment naive. For the ITT population (N=452), the 3-year PFS per IRF was 57.1% for patients on the A+CHP arm compared with 44.4% for patients on the CHOP arm, and the 3year OS was 76.8% for patients on the A+CHP arm compared with 69.1% for patients on the CHOP arm.

In line with the final therapeutic indication, which focuses on previously untreated systemic anaplastic large-cell lymphoma (sALCL), the sponsor provided subgroup analyses to that particular population. Patients with sALCL comprised 70% of the ECHELON-2 study's population, and in those patients the study showed a statistically significant PFS benefit (figure 1 below) and a clear OS trend in favour of A + CHP. It was also reported that the efficacy benefits of A+CHP over CHOP appear consistent regardless of prognostic factors like anaplastic lymphoma kinase (ALK) status, or patient's age. Therefore, it was considered that based on this data the significant benefit versus CHOP was established.

Figure 1. Kaplan Meier curve of PFS from ECHELON-2 in the sALCL population



With regards to the safety overview in the ALCL population, it was stated that within the ECHELON-2 study, A+CHP patients experienced a lower incidence of Grade 3 or higher AEs (59% vs 64%), serious adverse events (SAEs; 32% vs. 36%), discontinuations due to an AE (4% vs. 9%), and fatal AEs (3% vs. 10%), as compared to CHOP control arm. In patients aged 60 and older, the rate of febrile

neutropenia was higher regardless of treatment arm, which was mitigated with G-CSF primary prophylaxis.

Significant benefit versus CHOEP

The sponsor also further elaborated on the effects of A+CHP versus CHOEP. As regards efficacy, data from ECHELON-2 were compared to references used in the context of ESMO guidelines. The following table recapitulates the efficacy juxtaposition versus retrospective studies considering CHOEP and CHOP regimens. This indirect comparison was not considered as conclusive for any efficacy comparison in favour of the proposed product.

Table 1. Sourced from the sponsor's application.

Study	3-year PFS	3-year EFS	3-year OS
NLG-T-01 Phase 2 study (a) (d'Amore, Relander et al. 2012)			
sALCL	NA	NA	NA
ALK+ sALCL (n=0)	NA	NA	NA
ALK− sALCL (n=31)	68%	NR	78%
Swedish Registry (Ellin, Landstrom et al. 2014)			
sALCL	NR	NR	NR
ALK+ sALCL (n=68)	65%	NR	80%
ALK− sALCL (n=115)	37%	NR	45%
German High-Grade Lymphoma Study Group (Schmitz, Trumper et al. 2010)			
sALCL	NR	NR	NR
ALK+ sALCL (b) (n=78)	NR	76%	90%
ALK− sALCL (n=113)	NR	46%	62%
Nordic Lymphoma Group Study (Cederleuf, Jakobsen et al. 2017)			
sALCL	NA	NA	NA
ALK+ sALCL (n=122)	66%	NR	83%
ALK− sALCL (n=0)	NA	NA	NA
Czech Lymphoma Registry (Janikova, Chloupkova et al. 2019)			
sALCL			
ALK+ sALCL (n=57)	68%	NR	75%
ALK− sALCL (n=118)	43%	NR	49%
ECHELON-2 (A+CHP)			
sALCL (n=162)	65% (c)	NR	81%
Patients aged <60 (n=101)	73%	NR	85%
Patients aged ≥60 (n=61)	51%	NR	74%
ALK+ sALCL (n=49)	89%	NR	91%
Patients aged <60 (n=41)	90%	NR	92%
Patients aged ≥60 (n=8)	83%	NR	88%
ALK− sALCL (n=113)	55%	NR	77%
Patients aged <60 (n=60)	62%	NR	81%
Patients aged ≥60 (n=53)	47%	NR	72%

Note: Literature sources did not report sALCL analyses by age.
(a) 70% autologous stem cell transplantation rate and selection for transplant eligibility confound interpretation of study results.
(b) greater than 50% of the ALK+ sALCL population had favorable IPI 0-1.
(c) presented for patients with centrally confirmed sALCL diagnoses (n=163).
NA=not available, NR=not reported

It was stressed by the sponsor that the high haematologic toxicity of CHOEP renders it unsuitable for use in older or in general frail patients (Pfreundschuh, Blood 104(3):634-41). In particular for patients of more than 60 years of age, addition of etoposide is not recommended and CHOP remains the standard therapy for elderly PTCL patients (Schmitz et al, Blood 116(18):3418-3425).

In ECHELON-2, A+CHP showed a statistically significant improvement in both PFS, CR rate, ORR and OS as well as consistent, positive efficacy trends in duration of response and time to next treatment. These efficacy gains were associated with a safety profile that was manageable in patients of all ages.

It was therefore considered that A+CHP provides clinically significant benefit in terms of improved efficacy without additional dose limiting toxicity and can be used in all patients regardless of age.

The COMP accepted the argumentation and considered that the data from the ECHELON-2 trial discussed above justified significant benefit versus the recommended CHOP regimen and variant of CHOEP in the target population.

4. COMP position adopted on 23 April 2020

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 peripheral T-cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive sub-types;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Adcetris may be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The sponsor has presented data in first line systemic anaplastic large cell lymphoma patients, showing improved progression free survival in combination with cyclophosphamide, doxorubicin and prednisone (CHP) compared to the currently recommended regimen CHOP for the targeted patients. The Committee considered that this is 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 peripheral T-cell lymphoma (EU/3/08/595) is not removed from the Community Register of Orphan Medicinal Products.