ADCETRIS

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0111	Extension of indication for ADCETRIS to include treatment for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD), based on final results	25/04/2025	02/06/2025	SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	from phase 3 study HD21 (NCT02661503). This study is titled Treatment Optimization Trial in the First-Line Treatment of Advanced-Stage Hodgkin Lymphoma; Comparison of 4-6 Cycles of Escalated BEACOPP With 4-6 Cycles of BrECADD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the SmPC. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0113	Update of section 5.1 of the SmPC in order to update clinical information based on final results from ECHELON-1 final OS analysis data (C25003 CSR addendum 3). This is a randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma. In addition, the MAH took the opportunity to update the PI according to the Excipients Guideline and to introduce minor formatting changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/01/2025	02/06/2025	SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

IB/0114	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	13/12/2024	n/a		
IA/0115/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/11/2024	n/a		
IA/0112	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	08/08/2024	n/a		
II/0107	Extension of indication to include treatment of adult patients with previously untreated CD30+ Stage III Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine and dacarbazine (AVD), for ADCETRIS, based on the second interim analysis of OS data from ECHELON-1 study (C25003); this is a randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical HL. As a consequence, sections 4.1 and 5 of the SmPC are updated. Version 18.0 of the RMP has also been submitted. The variation leads to amendments to the Summary	14/09/2023	12/10/2023	SmPC	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-017'

	of Product Characteristics. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0110	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/08/2023	n/a		
IB/0108	B.II.z - Quality change - Finished product - Other variation	06/04/2023	n/a		
PSUSA/10039 /202208	Periodic Safety Update EU Single assessment - brentuximab vedotin	16/03/2023	n/a		PRAC Recommendation - maintenance
II/0103	Update of sections 4.8 and 5.1 of the SmPC to reflect new safety and efficacy information based on long-term data from the second interim analysis of OS (103 events) from study ECHELON-1, undertaken in previously untreated CD30+ Stage IV HL. In addition, following the completion of all specific obligations and considering the recent switch from a conditional to a full MA (variation II-99), the MAH takes the opportunity to propose the removal of the black triangle (regarding additional monitoring) from the SmPC and the Package Leaflet. Further, minor editorial changes are proposed in the SmPC and Package Leaflet and the contact details of the local representatives are being updated in the Package Leaflet.	17/11/2022	12/10/2023	SmPC and PL	Not applicable

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0105/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	24/10/2022	n/a		
II/0102/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting	01/09/2022	n/a		

	material [-] used in the manufacture of a biological/immunological product B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line) B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method				
IA/0104/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	31/08/2022	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
II/0099	Update of sections 4.8 and 5.1 of the SmPC, based on final results from study C25006, a multi-centre open-label, phase 4 study of 50 patients with r/r sALCL undertaken to further evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients who had previously received at least 1 multiagent chemotherapy regimen. This study was listed as an interventional category 2 PASS in the RMP (SOB 010). In addition, the MAH took the opportunity to request the granting of a marketing authorisation not subject to specific obligations and valid for five years, in accordance with Article 14-a(8) of Regulation (EC) No 726/2004, thereby deleting SOB 010 from the annex II and of the reference to the conditional marketing authorisation from annex II and the package leaflet. The revised RMP version 16.1 has also been submitted. An editorial update under section 5.1 of the SmPC (update of the ATC code) has been implemented. In addition, the CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that	24/03/2022	24/05/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion "Adcetris EMEA/H/C/002455/II/0099" For more information, please refer to the Summary of Product Characteristics.

	comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product for which the draft Summary of Product Characteristics is set out in Annex I. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0101/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	29/03/2022	13/04/2022	Annex II and PL	
IA/0100/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	11/03/2022	n/a		

	manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0093	Update of sections 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC based on the final results from study C25004, an open-label study in order to assess the safety and tolerability, of brentuximab vedotin when combined with multiagent chemotherapy regimen for first-line treatment of advanced-stage Hodgkin lymphoma in paediatric patients, in order to complete the PIP (P/0013/2021) and in order to fulfil Article 46 of Regulation EC No 1901/2006. The RMP version 16 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/11/2021	13/12/2021	SmPC	Please refer to Scientific Discussion EMEA/H/C/002455/II/0093. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10039 /202102	Periodic Safety Update EU Single assessment - brentuximab vedotin	14/10/2021	09/12/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10039/202102.
IA/0098	A.7 - Administrative change - Deletion of manufacturing sites	09/11/2021	n/a		

R/0090	Renewal of the marketing authorisation.	22/07/2021	16/09/2021		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0089	Submission of long-term follow-up data for clinical trial Echelon-2 (SGN035-014): A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphoma. The study is submitted to fulfil the post-approval-measure MEA 015.1. Section 5.1 of the SmPC has been updated to reflect this follow-up. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/09/2021	09/12/2021	SmPC	For more information, please refer to the Summary of Product Characteristics.
N/0092	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2021	09/12/2021	PL	
IA/0097	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	27/08/2021	n/a		

	manufacturer of a novel excipient				
IA/0096	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	10/08/2021	n/a		
IA/0095	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	06/08/2021	n/a		
IAIN/0094	B.I.e.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supportive data	27/07/2021	09/12/2021	Annex II	
II/0088/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a	24/06/2021	n/a		

	starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
II/0086	Update of the SmPC section 5.1 following the submission of the CSR addendum which includes long-term follow up or final OS results for the AETHERA study "A phase 3, randomised, double-blind, placebo-controlled, multicentre, clinical trial in patients with Hodgkin Lymphoma (HL) at risk of relapse or progression following ASCT" C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021	16/09/2021	SmPC	SmPC new text The MAH updated the brentuximab vedotin Summary of Product Characteristics (SmPC) to add long term follow up data from the recently closed randomized, blinded, placebo controlled phase 3 SGN35-005 AETHERA study conducted in patients with Hodgkin lymphoma (HL) who received an ASCT and whose HL demonstrated 1 or more risk factors for disease progression or relapse prior to ASCT. As of study closure, approximately 10 years after enrollment of the first patient, PFS per investigator continued to show a benefit (HR = 0.51 [95% CI (0.37, 0.71)]). Overall survival results were consistent with those reported at the time of primary analysis (HR = 1.11 [95% CI (0.72, 1.70)]). The hazard ratio for PFS per investigator for patients with 2 or more risk factors was 0.41 (95% CI [0.29, 0.58]). The hazard ratio for PFS per investigator for patients with 3 or more risk factors was 0.38 (95% CI [0.25, 0.59]). Overall survival results remained consistent with those observed as of the primary analysis. For more information, please refer to the Summary of

					Product Characteristics.
II/0085	Update of the SmPC section 5.1 following the 5 -year long-term follow up for the C25007 study in HL. Editorial updates have been also implemented in the PI. In addition, the MAH took the opportunity to update the list of local representatives for The Netherlands and United Kingdom (Northern Ireland) in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021	16/09/2021	SmPC and PL	SmPC new text The applicant has made some corrections in section 5.1. to include a description of patients' previous SCT status as according to the exclusion criteria for Study C25007, patients must not have received prior autologous or allogeneic SCT. Clarifications on the dose and posology of Adcetris in clinical trials have been introduced in section 5.1. For more information, please refer to the Summary of Product Characteristics.
IB/0087	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	19/04/2021	n/a		
PSUSA/10039 /202002	Periodic Safety Update EU Single assessment - brentuximab vedotin	15/10/2020	14/12/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10039/202002.
IA/0084	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	19/11/2020	n/a		
IB/0081	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/09/2020	14/12/2020	Annex II	
R/0079	Renewal of the marketing authorisation.	23/07/2020	15/09/2020		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and

					having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IAIN/0083	A.1 - Administrative change - Change in the name and/or address of the MAH	02/09/2020	14/12/2020	SmPC, Labelling and PL	
IB/0082	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	01/09/2020	n/a		
SW/0074	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0022	28/05/2020	23/07/2020	SmPC and Annex II	The following is described regarding the safety profile in elderly treated with brentuximab vedotin monotherapy in SmPC section 4.8: "The safety profile in elderly patients was consistent with that of adult patients". Based on the information provided by the MAH, this statement is not considered adequate. The incidences of pneumonia, febrile neutropenia and neutropenia were shown to be considerable different for patients ≥65 years as compared to patients <65 years. Furthermore, as also mentioned by the MAH older age is an important risk factor for, among others, the occurrence of neutropenia and febrile neutropenia. Therefore, in view of available data regarding the PASS final study report, the PRAC Rapporteur considered that changes to the product information were warranted.
IAIN/0080	C.I.11.a - Introduction of, or change(s) to, the	17/07/2020	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority				
II/0075/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	28/05/2020	n/a		
II/0070	Extension of indication to include in combination with cyclophosphamide, doxorubicin, and prednisone treatment of adults with previously untreated CD30+ sALCL for Adcetris; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are being updated to reflect the indication. The Package Leaflet (PL) is updated in accordance. Version 15.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) -	26/03/2020	12/05/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Adcetris-H-C-2455-II-0070'.

	Addition of a new therapeutic indication or modification of an approved one				
IB/0077	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	16/04/2020	n/a		
IB/0076/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	14/04/2020	n/a		
IB/0073/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/03/2020	n/a		

R/0067	Renewal of the marketing authorisation.	25/07/2019	19/09/2019		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0071	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/09/2019	n/a		
PSUSA/10039 /201902	Periodic Safety Update EU Single assessment - brentuximab vedotin	05/09/2019	n/a		PRAC Recommendation - maintenance
II/0069	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	25/07/2019	n/a		
II/0066	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	25/07/2019	n/a		
IB/0065/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/04/2019	n/a		

	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IB/0064/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol	12/03/2019	n/a		
IB/0063	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	28/02/2019	n/a		
IA/0062/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/02/2019	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0055	Extension of the existing Hodgkin lymphoma (HL) indication to include the frontline treatment of adult patients with CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine (AVD), based on data from ECHELON-1 (C25003), a phase 3 multi-centre, randomised, open-label study comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin, doxorubicin, vinblastine and dacarbazine versus the mPFS obtained with doxorubicin, bleomycin, vinblastine and dacarbazine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10. The MAH also submitted an updated RMP version 15, implementing Revision 2 of the EU-RMP template. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	13/12/2018	06/02/2019	SmPC, Labelling and PL	Please refer to the Scientific Discussion – Adcetris II-55.
II/0061	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a	17/01/2019	n/a		

	biol/immunol method				
II/0056/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	13/09/2018	n/a		
R/0058	Renewal of the marketing authorisation.	26/07/2018	10/09/2018		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II

					to the opinion.
PSUSA/10039 /201802	Periodic Safety Update EU Single assessment - brentuximab vedotin	06/09/2018	n/a		PRAC Recommendation - maintenance
IB/0059/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	06/08/2018	n/a		
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/07/2018	10/09/2018	Labelling	
II/0049	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with data from study C25002; a phase 1/2 study of brentuximab vedotin (SGN-35) in paediatric patients with relapsed or refractory systemic anaplastic large cell lymphoma or Hodgkin's lymphoma (listed in the agreed PIP covering the conditions of Hodgkin	11/01/2018	10/09/2018	SmPC	The pharmacokinetics of brentuximab vedotin in paediatric patients show a multi-exponential decline in antibody-drug conjugate (ADC) serum concentrations with a terminal half-life of approximately 4 to 5 days. Exposures were approximately dose proportional with a trend observed for lower ADC exposures at lower ages/ body weights in the

	lymphoma and anaplastic large cell lymphoma for ADCETRIS (EMEA-000980-PIP01-10-M04)). An updated RMP version 12.3 was provided as part of the application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				study population. Median ADC AUC in children and adolescents from this study was approximately 14% and 3% lower than in adult patients, respectively, while monomethyl auristatin E (MMAE) exposures were 53% lower and 13% higher, respectively, than in adult patients. There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for anti-drug antibodies (ADAs). No patients aged <12 years and 2 patients aged ≥12 became persistently ADA positive. The overall response rate was 47% in response-evaluable patients with relapsed or refractory Hodgkin's lymphoma (r/r HL), 53% in patients with relapsed or refractory systemic anaplastic large cell lymphoma (r/r sALCL) and 60% in sALCL patients in first relapse. No new safety concerns were reported. The available data is too limited to support posology recommendations in the paediatric population.
II/0048	Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy", based on data from study C25001 (the 'ALCANZA' study): "A Phase 3 Trial of brentuximab vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP (version 10.1) has also been submitted.	09/11/2017	15/12/2017	SmPC and PL	Please refer to the Scientific Discussion – Adcetris II-48.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
R/0051	Renewal of the marketing authorisation.	14/09/2017	10/11/2017	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0054/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/10/2017	n/a		
PSUSA/10039 /201702	Periodic Safety Update EU Single assessment - brentuximab vedotin	28/09/2017	n/a		PRAC Recommendation - maintenance
IB/0053	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	19/09/2017	n/a		
II/0043	Update of sections 4.8 and 5.1 of the SmPC to reflect the final study results from study C25007: a single-	20/07/2017	10/11/2017	SmPC and Annex II	Study C25007 is a phase 4 single-arm study was conducted in patients with relapsed or refractory Hodgkin lymphoma

	arm study of brentuximab vedotin in patients with relapsed or refractory hodgkin lymphoma who are not suitable for stem cell transplantation or multiagent chemotherapy. The submission of the clinical study report fulfils SOB 011 of the conditional marketing authorisation for Adcetris Annex II is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(HL) (n=60) who had received at least 1 prior chemotherapeutic regimen and at the time of treatment initiation with brentuximab vedotin were not considered candidates for stem cell transplant (SCT) or multiagent chemotherapy. The median number of cycles was 7 (range, 1 to 16 cycles). Patients were treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks. Per review facility, the overall response rate (ORR) in the ITT population was 50% (95% CI [37%, 63%]). A best overall response of complete remission (CR) was reported for 7 patients (12%); partial remission (PR) was reported for 23 patients (38%). Among these 30 patients, the median time to response, defined as the time from first dose to the soonest of PR or CR, was 6 weeks (range, 5 to 39 weeks). The median time to best overall response, defined as the time from first dose to the clinical best response of CR or PR, was 11 weeks (range, 5 to 60 weeks). Twenty-eight patients (47%) went on to receive SCT after a median of 7 cycles (range, 4 to 16 cycles) of brentuximab vedotin treatment. The 32 patients (53%) who did not receive subsequent SCT also received brentuximab vedotin for a median of 7 cycles (range, 1 to 16 cycles). Of the study’s 60 patients, 49 patients (82%) received >1 prior cancer-related treatment and 11 patients (18%) received 1 prior cancer-related treatment. Per review facility, the ORR was 51% (95% CI [36%, 66%]) for the patients who had received >1 prior cancer-related treatment and 45% (95% CI [17%, 77%]) for the patients who had received 1 prior cancer-related treatment. For the patients who received >1 prior cancer-related treatment, a

					best overall response of CR was reported for 6 patients (12%); PR was reported for 19 patients (39%). For the patients who received 1 prior cancer-related treatment, CR was reported for 1 patient (9%) and PR was reported for 4 patients (36%). Out of the 49 patients receiving >1 line of prior treatment, 22 patients (45%) received subsequent SCT; of the 11 patients who had received 1 prior treatment, 6 patients (55%) received subsequent SCT. No new safety concerns were identified in study C25007.
IAIN/0052	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/07/2017	10/11/2017	SmPC and PL	
II/0045	Update of section 5.1 of the SmPC in order to add 5-year follow-up overall survival (OS) data from patients included in study SG035-0004, a phase 2 open-label study of brentuximab vedotin in the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL), in accordance with the specific obligation SOB 028. Annex II of the product information and the RMP (version 9.0) are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/06/2017	10/11/2017	SmPC and Annex II	Information on progression-free survival (PFS) and objective response rate (ORR) was updated to add 5-year follow-up overall survival (OS) data from patients included in study SG035-0004, a phase 2 open-label study of brentuximab vedotin in the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL). Overall survival at 5 years is 60% and median progression-free survival is 14.6 months.
IB/0046/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	11/05/2017	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IA/0047/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	28/04/2017	n/a		
II/0041/G	This was an application for a group of variations. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	16/02/2017	n/a		

	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.II.h.1.b.2 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier - without modifications of risk assessment				
IB/0044	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2017	10/11/2017	Annex II	
IB/0042/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	04/01/2017	n/a		
IAIN/0040	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	14/11/2016	10/11/2017	Annex II and PL	
R/0035	Renewal of the marketing authorisation.	21/07/2016	21/10/2016		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and

					having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
PSUSA/10039 /201602	Periodic Safety Update EU Single assessment - brentuximab vedotin	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0037	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	02/08/2016	n/a		
IB/0038	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	28/06/2016	21/10/2016	SmPC	
II/0025	Extension of Indication to include the treatment of adult patients with Hodgkin Lymphona (HL) at increased risk of relapse or progression following autologous stem cell transplantation (ASCT). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (v.6.3) are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	26/05/2016	24/06/2016	SmPC and PL	Please refer to the scientific discussion Adcetris EMEA/H/C/002455/II/25 for further information.

	modification of an approved one				
II/0033	Update of sections 4.5 and 5.2 of the SmPC in order to reflect clinical pharmacology data from study C25005. The provision of the final CSR for study C25005 addresses the post-authorisation measure MEA 013. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	24/06/2016	SmPC	Monomethyl auristatin E (MMAE) is the major active metabolite of brentuximab vedotin. In Study C25005 the company has evaluated the exposure to MMAE and its metabolites in the absence and presence of rifampicin, after administration of multiple doses of brentuximab vedotin, in patients with relapsed or refractory Hodgkin lymphoma (HL). Though PK data are limited, co administration of rifampicin appeared to reduce plasma concentrations of MMAE metabolites that could be assayed. MMAE is further metabolized mainly to an equally potent metabolite; however, its exposure is an order of magnitude lower than that of MMAE. Thus, it is not likely to have any substantial contribution to the systemic effects of MMAE. Overall, the safety findings for the 20 adult patients in Study C25005 were consistent with the known toxicity profile of brentuximab vedotin. No new safety signals were observed.
II/0030/G	This was an application for a group of variations. Update of section 4.4 of the SmPC in order to add a warning on hepatotoxicity, further to the outcome of the PSUR assessment (PSUSA 010039-201502). The Package Leaflet and RMP (version 6.2) are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Update of section 4.4 of the SmPC in order to add a warning on gastrointestinal complications. The	28/04/2016	24/06/2016	SmPC and PL	The most frequently observed adverse reactions in the pivotal phase 2 population were: peripheral sensory neuropathy, fatigue, nausea, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, and vomiting. Adverse reactions that led to treatment discontinuation in two or more Hodgkin Lymphoma or systemic Anaplastic Large Cell Lymphoma patients were peripheral sensory neuropathy, peripheral motor neuropathy, demyelinating polyneuropathy, and recurrent Hodgkin's disease. Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress

	Package Leaflet and RMP are updated accordingly. Update of section 4.4 of the SmPC in order to update a warning on pulmonary toxicity, providing examples of pulmonary toxicity diagnoses. The Package Leaflet and RMP are updated accordingly. Update of section 4.8 of the SmPC in order to implement data from the pivotal Phase II studies. The RMP is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding brentuximab vedotin dosing during evaluation and until symptomatic improvement. Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately. Hepatotoxicity in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with brentuximab vedotin. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk. Liver function should be tested before initiating the treatment and routinely monitored in patients receiving brentuximab vedotin. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of brentuximab vedotin.
II/0032	Update of SmPC section 5.1 to include 5-year observed survival data from the SGN035-0003 study	01/04/2016	24/06/2016	SmPC	The median overall survival (OS) was 40.5 months (the median observation time (time to death or last contact)

	in patients with relapsed or refractory Hodgkin lymphoma. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				from first dose was 35.1 months (range 1.8 to 72.9+ months). The estimated overall survival rate at 5 years was 41% (95% CI [31%, 51%]). The median duration of objective response (DOR) per IRF was 6.7 months (95% CI: 3.6, 14.8) and the range was 1.2+ months to 43+ months. For patients with a best response of complete remission (CR), the median DOR per IRF by Kaplan-Meier analysis was 27.9 months (95% CI: 10.8, -). Of the patients treated, 8 responding patients went on to receive an allogeneic SCT.
IB/0034/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/03/2016	24/06/2016	Annex II	
IG/0652	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	22/01/2016	n/a		
IAIN/0029/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	21/12/2015	24/06/2016	Annex II and PL	

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
II/0028	Update of sections 4.2, 4.4, 4.8 and 5.1 of the 50 mg powder for concentrate for solution SmPC based on the results of study SGN35-006 Part A, to allow retreatment of adult patients who have responded to previous treatment with brentuximab vedotin under the existing indications. In addition, the MAH took the opportunity to bring the SmPC and Annex II in line with the latest QRD template version 9.1. A revised RMP version 5.3 was agreed during the procedure. The requested variation proposed amendments to the Summary of Product Characteristics (SmPC), Annex II and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/10/2015	19/11/2015	SmPC and Annex II	Study SGN35-006 (Retreatment Study) The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with brentuximab vedotin was evaluated in a phase 2, open-label, multicenter trial. Twenty patients with relapsed or refractory HL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 7 (range, 2 to 37 cycles). Of the 20 evaluable patients with HL, 6 patients (30%) achieved a CR and 6 patients (30%) achieved a PR with brentuximab vedotin retreatment, for an ORR of 60%. The median duration of response was 9.2 and 9.4 months in patients who achieved OR (CR+PR) and CR, respectively. Seven patients with relapsed sALCL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 8.5 (range, 2 to 30 cycles). Of the 8 sALCL patients, 3 were retreated twice for a total of 11 retreatment experiences. Retreatment with brentuximab vedotin resulted in 6 CRs (55%) and 4 PRs (36%), for an ORR of 91%. The median duration of response was 8.8 and 12.3

					months in patients who achieved OR (CR+PR) and CR, respectively. The types and rates of adverse reactions reported for patients retreated with ADCETRIS were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 1 or 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies. The incidence of pre-existing peripheral neuropathy in patients with relapsed or refractory HL or sALCL who were retreated with brentuximab vedotin was 48%. Treatment emergent neuropathy occurred in 69% of the population. At the time of last evaluation, the majority of patients who were retreated and experienced treatment-emergent peripheral neuropathy (80%) had improvement or resolution of their peripheral neuropathy symptoms. Peripheral neuropathy led to discontinuation in 21% and dose modifications in 34% of patients who were retreated. In view of these data, the recommended starting dose for the retreatment of patients with relapsed or refractory HL or sALCL who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose.
PSUSA/10039 /201502	Periodic Safety Update EU Single assessment - brentuximab vedotin	10/09/2015	n/a		PRAC Recommendation - maintenance
R/0026	Renewal of the marketing authorisation.	23/07/2015	10/09/2015		The CHMP, having reviewed the available information on

					the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion
PSUSA/10039 /201408	Periodic Safety Update EU Single assessment - brentuximab vedotin	12/03/2015	n/a		PRAC Recommendation - maintenance
IAIN/0024	A.1 - Administrative change - Change in the name and/or address of the MAH	02/03/2015	03/07/2015	SmPC, Labelling and PL	
IB/0023	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/02/2015	n/a		
II/0020	To add manufacturer of the Active Substance (AS) B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	20/11/2014	03/07/2015	Annex II	
PSUV/0019	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
R/0017	Renewal of the marketing authorisation.	26/06/2014	22/08/2014		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the

					opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
II/0012	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to present updated advice to physicians on treatment with Adcetris of patients with hepatic or renal impairment based on data from study SGN-35-008b. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	22/08/2014	SmPC and PL	Study SGN35-008 evaluated the pharmacokinetic of brentuximab and antimicrotubule agent monomethyl auristatin E (MMAE) after administration of 1.2 mg/kg of Adcetris to patients with hepatic impairment and to patients with renal impairment. Pharmacokinetic data from this study were submitted to support the proposal for an updated advice to physicians on treatment of patients with hepatic or renal impairment. Available data indicate that antimicrotubule agent monomethyl auristatin E (MMAE) clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations. Compared to patients with normal renal function, MMAE exposure increased approximately 1.9-fold in patients with severe renal impairment (creatinine clearance < 30 ml/min) and no effect was observed in patients with mild or moderate renal impairment; compared to patients with normal hepatic function, MMAE exposure increased approximately 2.3- fold in patients with hepatic impairment. The proposed recommended starting dose in patients with severe renal impairment and in patients with hepatic impairment is 1.2 mg/kg is therefore considered acceptable.
II/0018	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	03/07/2015	SmPC and PL	

IB/0015/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same	13/05/2014	n/a		

	pharmaceutical group as the currently approved manufacturer B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0016	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/04/2014	n/a		
II/0010	Update of sections 4.4 and 4.8 of the SmPC in order to include the common adverse drug reaction 'Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased' under Hepatobiliary disorders following a PRAC recommendation and 'sepsis/septic shock' to ensure alignment with the RMP, where 'infections including bacteraemia, sepsis and septic shock' is already an important identified risk. The Package Leaflet is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	20/03/2014	22/08/2014	SmPC and PL	Further to a PRAC recommendation the MAH provided a cumulative review on the risk of hepatotoxicity associated with brentuximab vedotin treatment. Based on this safety evaluation the MAH proposed the inclusion of 'Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased' as a common adverse drug reaction under hepatobiliary disorders. The MAH took the opportunity to include the risk of sepsis/septic shock in the SmPC to ensure alignment with RMP. The MAH's proposal to minimise these risks was endorsed by CHMP.
PSUV/0013	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
IG/0401	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the	11/02/2014	n/a		

	PSMF location				
II/0011	Update of section 5.1 of the SmPC in order to reflect the updated overall survival (OS) and Progression Free survival (PFS) analyses from both pivotal studies SG035-0003 and SG035-0004 in Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) patients respectively. Annex II has been updated accordingly to remove part of the SOB-001. In addition, the MAH took the opportunity to add the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/01/2014	22/08/2014	SmPC, Annex II and PL	Based on the updated results of SG035-0003 study in Hodgkin lymphoma (HL) patients the median overall survival (OS) is 40.5 months (the median observation follow-up time (time to death or last contact) from first dose was 32.7 months). An exploratory intra-patient analysis showed that approximately 64% of the HL and the sALCL patients treated with brentuximab vedotin as part of the SG035- 0003 and SG035-0004 clinical study studies, respectively, experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy. Based on the updated results of SG035-0004 study in systemic anaplastic large cell lymphoma (sALCL) patients the estimated 36 month overall survival was 63% (the median observation follow-up time (time to death or last contact) from first dose was 33.4 months). An exploratory intra-patient analysis showed that approximately 69% of the HL and the sALCL patients treated with brentuximab vedotin as part of the SG035-0003 and SG035-0004 clinical study studies, respectively, experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy. Section 5.1 of the SmPC has been updated to reflect the above results. In addition Annex II of the PI has been updated to reflect the partial fulfilment of the SO-001.
II/0009	Update of section 4.6 of the SmPC to extend the recommendation of contraception for women of childbearing potential during treatment with	23/01/2014	22/08/2014	SmPC and PL	Brentuximab vedotin causes teratogenicity and embryo-foetal lethality in animals and therefore women should avoid pregnancy during treatment. Further to a review of

	brentuximab vedotin from 30 days to 6 months after treatment, further to a review of the protocols of studies with brentuximab vedotin and of existing recommendations for other antineoplastic chemotherapies with a similar mechanism of action. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the protocols for studies with brentuximab vedotin and of existing recommendations for other antineoplastic chemotherapies with a similar mechanism of action, the recommendation to women of childbearing potential to use two methods of effective contraception during treatment with brentuximab vedotin has been extended from 30 days to until 6 months after treatment.
II/0008	Update of section 4.4 of the SmPC in order to add a warning regarding the risk of pulmonary toxicity further to a PRAC recommendation following the review of a signal identified in Eudravigilance. The Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/11/2013	22/08/2014	SmPC, Annex II, Labelling and PL	Based on the cumulative review on pulmonary toxicity describing 41 spontaneously reported cases, the PRAC considered that the risk of pulmonary toxicity associated with the use of brentuximab vedotin cannot be ruled out at this time and therefore the PRAC recommended the inclusion of pulmonary toxicity as warning in the SmPC. The MAH proposed the addition of a warning to reflect the risk of pulmonary toxicity in section 4.4 of the SmPC which was endorsed by CHMP.
II/0007	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information related to the new important potential risk of acute pancreatitis. The Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and	21/11/2013	22/08/2014	SmPC, Annex II, Labelling and PL	Based on the cumulative review of all available data for events of acute pancreatitis to a data lock point (DLP) of 27 June 2013, the MAH considered that acute pancreatitis is a new and important potential risk associated with brentuximab vedotin therapy. Therefore sections 4.4 and 4.8 of the SmPC have been updated to include safety information related to the new important potential risk of acute pancreatitis.

	Veterinary Medicinal Products - Other variation				
T/0006	Transfer of Marketing Authorisation	04/10/2013	24/10/2013		
R/0005	Renewal of the marketing authorisation.	27/06/2013	26/08/2013	SmPC, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Adcetris, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IAIN/0004	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	08/05/2013	26/08/2013	Annex II and PL	
IAIN/0003	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/03/2013	n/a		
II/0002	Update of section 4.8 of the SmPC in order to clarify the sources of the safety data (adverse drug reactions) presented, and to add the adverse reactions of progressive multifocal leukoencephalopathy (PML), anaphylactic reactions and febrile neutropenia that occurred outside of the phase 2 pivotal studies in the tabulated list of adverse reactions. The Package Leaflet has been updated accordingly. Furthermore, the MAH has taken this opportunity to bring the PI in line with the latest QRD template	21/02/2013	26/08/2013	SmPC, Annex II and PL	In this variation section 4.8 of the SmPC has been updated in order to clarify the sources of the safety data presented. The safety profile of ADCETRIS is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. In addition, adverse drug reactions solely reported outside of the phase 2 population which were described as selected events of interest have now been also included in Table 3 under the frequency category “not known” (cannot be estimated from the available data). The Package Leaflet has been updated accordingly.

	version 8.3 and to implement minor editorial changes. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0001/G	This was an application for a group of variations. B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	21/12/2012	n/a		