Darzalex

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/0049/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	22/07/2021		SmPC, Annex II, Labelling and PL	

[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).

	B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
II/0048/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.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	24/06/2021	n/a		
II/0044	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/05/2021	21/06/2021	SmPC and PL	

II/0043	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/05/2021	21/06/2021	SmPC and PL	
II/0047	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/05/2021	21/06/2021	SmPC, Labelling and PL	
PSUSA/10498 /202011	Periodic Safety Update EU Single assessment - daratumumab	06/05/2021	n/a		PRAC Recommendation - maintenance
II/0040	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	14/01/2021	n/a		
IB/0045	B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	17/12/2020	n/a		
II/0041	Update of section 4.8 of the SmPC in order to include CMV infections as a new adverse drug reaction (ADR) with frequency common following a comprehensive, cross-program evaluation of all potential cases of treatment-emergent cytomegalovirus (CMV) infections with use of daratumumab. The Package Leaflet is updated accordingly. Several minor linguistic improvements are also proposed. C.I.4 - Change(s) in the SPC, Labelling or PL due to	03/12/2020	21/06/2021	SmPC, Labelling and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0042	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	05/11/2020	n/a		
II/0038	Update section 4.8 of the SmPC in order to add sepsis with frequency common as an ADR and incidence data on fatal infections and adverse reactions in the elderly patients based on cross-programmatic review of data. The MAH also proposed minor corrections in section 4.8 of the SPC. The Package Leaflet and labelling is updated accordingly. Correction of Annex II to add the active substance manufacturer "Samsung Biologics, Korea", which was overlooked during procedure II-018 (approved on 11 July 2019) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/07/2020	21/06/2021	SmPC, Annex II, Labelling and PL	SmPC new text: Section 4.8 Sepsis is added to the list of adverse drug reactions (ADRs) in safety summary profile and in table 5 with frequency common Information was added on the incidence of a) fatal infections in patients receiving DARZALEX combination therapy b) adverse reactions in the elderly patients For more information, please refer to the Summary of Product Characteristics.
II/0039	Update of section 5.1 of the SmPC in order to update information regarding immunogenicity following completion of post-authorization commitments regarding re-analysis of all ADA samples taken from previously submitted clinical using the Enhanced DT Method (previously developed as a result of PAM-MEA-005). The Important Potential Risk of	11/06/2020	21/06/2021	SmPC	SmPC new text Section 5.1. Immunogenicity In patients treated with subcutaneous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies. For more information, please refer to the Summary of

	immunogenicity is removed from the RMP and version 6.5 is submitted C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				Product Characteristics.
PSUSA/10498 /201911	Periodic Safety Update EU Single assessment - daratumumab	11/06/2020	n/a		PRAC Recommendation - maintenance
X/0032	Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration	30/04/2020	03/06/2020	SmPC, Annex II, Labelling and PL	
IB/0036	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	30/03/2020	n/a		
II/0035	Update of section 5.1 of the SmPC in order to update efficacy information based on interim results from phase III follow up studies of 3 approved combination treatments of daratumab (D) in relapsed or refractory MM patients MMY3003 (DRd vs	26/03/2020	03/06/2020	SmPC and PL	In Study MMY3007: Results of an updated PFS analysis after a median follow up of 40 months continued to show an improvement in PFS for patients in the D VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D VMP arm and 19.3 months in the VMP arm

	Rd) and MMY3004 (DVd vs Vd) and in newly diagnosed MM patients MMY3007 (DVd vs Vd). In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce some minor editorial changes in the PI and to update the list of local representatives for Italy in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(HR=0.42; 95% CI: 0.34, 0.51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D VMP. D VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D VMP arm. Median OS was not reached for either arm In Study MMY3003: Results of an updated PFS analysis after a median follow up of 55 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with DRd In Study MMY3004: Results of an updated PFS analysis after a median follow up of 50 months continued to show an improvement in PFS for patients in the DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with DVd versus Vd For more information, please refer to the Summary of Product Characteristics.
II/0030	Extension of indication in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT) for Darzalex; as a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of	12/12/2019	20/01/2020	SmPC and Labelling	Please refer to the Scientific Discussion Darzalex-H-C-4077-II-0030

	the SmPC are updated. The Package Leaflet is updated in accordance. The RMP (version 6.4) has also been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0034	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/11/2019	n/a		
II/0033	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/11/2019	n/a		
II/0029	Extension of indication in combination with lenalidomide and dexamethasone (Rd) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) for Darzalex; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP has been updated accordingly (finally agreed version 6.2). Furthermore, the Annex II is brought in line with the latest QRD template version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/10/2019	19/11/2019	SmPC, Annex II and PL	Please refer to the Scientific Discussion Darzalex-H-C-4077-II-0029

II/0018/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.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	11/07/2019	n/a		
II/0027	Update of sections 4.4 and 4.8 of the SmPC to introduce a new warning and to add the recently identified risk of Hepatitis B reactivation as an uncommon adverse drug reaction, respectively. The PL and the RMP (v. 5.0 rev2) are amended accordingly. A DHPC to inform prescribers on the newly identified risk has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/05/2019	28/06/2019	SmPC and PL	Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment with DARZALEX. For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of DARZALEX treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated. In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

PSUSA/10498 /201811	Periodic Safety Update EU Single assessment - daratumumab	14/06/2019	n/a		PRAC Recommendation - maintenance
IB/0031	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	29/04/2019	n/a		
IB/0028	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	08/04/2019	n/a		
II/0020	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	n/a		
IB/0025/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	18/12/2018	n/a		
II/0019	Update of sections 4.2, 4.8 and 5.2 of the SmPC in order to include the possibility for a split first dose for the treatment of patients with multiple myeloma, based on the Phase 1b open-label, non-randomised, multicentre Study 54767414MMY1001. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	15/11/2018	18/12/2018	SmPC and PL	In Study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of

	new quality, preclinical, clinical or pharmacovigilance data				a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions. Simulation of daratumumab pharmacokinetics was conducted for all recommended dosing schedules in 1,309 patients with multiple myeloma. The simulation results confirmed that the split and single dosing for the first dose provide similar PK, with the exception of the PK profile in the first day of the treatment. In conclusion and in order to facilitate administration, the first prescribed 16 mg/kg dose of daratumumab at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2, respectively.
II/0023	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	13/12/2018	n/a		
IB/0022	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	30/11/2018	28/06/2019	SmPC, Labelling and PL	
PSUSA/10498 /201805	Periodic Safety Update EU Single assessment - daratumumab	29/11/2018	n/a		PRAC Recommendation - maintenance

N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	18/12/2018	PL	
II/0011	Extension of Indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant for Darzalex; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 3.2 (in version 2 of the RMP template). In addition, the Marketing authorisation holder took the opportunity to update Annex II with regards to PSUR requirements and to update the contact details of the Lithuanian and Slovenian local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/07/2018	31/08/2018	SmPC and PL	Please refer to the Scientific Discussion – Darzalex II-11.
PSUSA/10498 /201711	Periodic Safety Update EU Single assessment - daratumumab	14/06/2018	n/a		PRAC Recommendation - maintenance
IAIN/0016/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	18/05/2018	n/a		

	changes to an approved test procedure B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
II/0013	Update of section 4.8 of the Darzalex SmPC in order to add anaphylactic reactions with a frequency 'rare' as new adverse reactions and update of section 4.4 to complement the existing warning on infusion related reactions based on the cumulative review of clinical trial and post-marketing data. The Package Leaflet (PL) is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to add in section 4.4 the traceability statement of biological medicines to bring the product information in line with the guideline on good pharmacovigilance practices and to add specific text relating to the excipient sodium to align the product information with the updated published EMA EU excipient guideline. The MAH also took the opportunity to update the PL with revised contact details of local representative for Czech Republic and Portugal. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/05/2018	31/08/2018	SmPC and PL	Darzalex can cause serious infusion related reactions (IRRs), including anaphylactic reactions. All patients should be monitored throughout the infusion for IRRs. For patients that experience any Grade IRRs, continue monitoring post-infusion until symptoms resolve. In clinical trials IRRs were reported in approximately half of all patients treated with Darzalex. The majority of IRRs occurred at the first infusion and were Grade 1-2. Patients should be pre medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with Darzalex. Darzalex infusion should be interrupted for IRRs of any severity and medical management/supportive treatment for IRRs should be instituted as needed. For patients with Grade 1, 2, or 3 IRRs, the infusion rate should be reduced when re starting the infusion. If an anaphylactic reaction or life threatening (Grade 4) infusion reaction occurs, appropriate emergency resuscitation should be initiated immediately. Darzalex therapy should be discontinued immediately and permanently.
II/0014	Update of section 4.5 of the SmPC in order to add information relating to the daratumumab interference with Serum Protein Electrophoresis	15/03/2018	25/06/2018	SmPC	Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins

	(SPE) and Immunofixation (IFE) assays and the daratumumab-specific immunofixation reflex assay (DIRA). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.
IB/0012	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	21/12/2017	n/a		
PSUSA/10498 /201705	Periodic Safety Update EU Single assessment - daratumumab	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0010	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/09/2017	n/a		
IB/0008/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data 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.b.5 - Stability of FP - Extension of the shelf	02/08/2017	25/06/2018	SmPC	

	life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IA/0007/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 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)	16/06/2017	25/06/2018	Annex II	
PSUSA/10498 /201611	Periodic Safety Update EU Single assessment - daratumumab	09/06/2017	n/a		PRAC Recommendation - maintenance
II/0002	Extension of Indication for Darzalex in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC are updated in order to update the information on the target patient population, posology, warnings, interactions, efficacy and pharmacokinetics. A new warning is introduced in	23/02/2017	28/04/2017	SmPC, Annex II and PL	Please refer to the Scientific Discussion Darzalex EMEA/H/C/004077/II/0002.

	section 4.4 regarding neutropenia/thrombocytopenia induced by background therapy. Furthermore, the CHMP is of the opinion that all specific obligations have been fulfilled following submission of the final results of studies MMY3003 and MMY3004 and in light of the data generated and the evidence of compliance with the specific obligations, the CHMP recommends the granting of a marketing authorisation in accordance with Article 14(1) of Regulation No 726/2004. Annex II is updated to remove the fulfilled specific obligations. The Package Leaflet and Risk Management Plan (RMP version 2.1) are updated in accordance. In addition, the Marketing authorisation holder (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 modification of an approved one				
R/0003	Renewal of the marketing authorisation.	23/02/2017	24/04/2017		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations assessed through variation II-02 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. Furthermore, in the framework of the variation II-02, the CHMP concludes that the remaining specific obligations for the Conditional Marketing Authorisation are fulfilled and recommends granting a Marketing Authorisation no longer

					subject to specific obligations.
II/0005/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study	06/04/2017	n/a		
II/0004	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	23/02/2017	n/a		
IA/0001/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	01/09/2016	n/a		