Dupixent

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/0079	Extension of indication for DUPIXENT to include treatment of adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist	30/05/2024	28/06/2024	SmPC and PL	Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-Var.0079'.

[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).

	(LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate, based on final results from study EFC15804 (BOREAS) and interim results from study EFC15805 (NOTUS); these are phase 3, randomized, double blind, placebo-controlled, multi-center, parallel group, 52-week studies to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with elevated blood eosinophils (i.e. ≥300 cells/microliter). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 10.3 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. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2024		Labelling	
IB/0087	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a	14/06/2024	n/a		

	biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
II/0078	Update of sections 4.2 of the SmPC in order to allow the use of the Dupixent Prefilled Pen presentations for patients aged 2 to < 12 years of age based on final results of the R668-AD-1434 sub-study; this is an interventional open-label sub-study which purpose is to evaluate the PK, safety, immunogenicity, and efficacy of repeat doses of dupilumab (200 mg Q4W, 300 mg Q4W, and 200 mg Q2W) administered SC using a PFP with a skin pinch in children ≥2 to <12 years of age. The Package Leaflet is updated accordingly. In addition, the MA took the opportunity to update 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	21/03/2024	19/04/2024	SmPC and PL	The applicant supported the introduction of the pre-filled pen (PFP) for patients aged 2 to < 12 years of age with the final results of R668-AD-1434 sub-study. Based on the provided data on pharmacokinetics, safety, immunogenicity, and efficacy of repeat doses of Dupixent, there are no new safety findings or differences between age and weight cohorts. The safety profile is consistent with the known safety profile of Dupixent. The administration via PFP seems to be well tolerated in children aged ≥2 to <12 years. In conclusion, the study results substantiate the safe and efficient use of the PFP in patients ≥2 to <12 years. For more information, please refer to the Summary of Product Characteristics.
IA/0085	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	08/04/2024	28/06/2024	SmPC, Labelling and PL	
IB/0084/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits	05/04/2024	n/a		

	applied during the manufacture of the AS - Tightening of in-process limits B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IB/0082	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	02/02/2024	n/a		
IB/0080/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	12/12/2023	n/a		
IB/0076/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.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.I.a.2.a - Changes in the manufacturing process of	30/11/2023	n/a		

	the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
PSUSA/10645 /202303	Periodic Safety Update EU Single assessment - dupilumab	26/10/2023	n/a		PRAC Recommendation - maintenance
IB/0077	B.IV.1.z - Change of a measuring or administration device - Other variation	13/10/2023	n/a		
II/0072	Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update the safety and efficacy information relevant to patients with hand and foot Atopic Dermatitis based on the results from study R668-AD-1924. This is a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Moderate-to-Severe Atopic Hand and Foot Dermatitis. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/08/2023	19/04/2024	SmPC	The efficacy and safety of dupilumab have been assessed in a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled R668-AD-1924 study investigating the efficacy and safety of dupilumab monotherapy over 16 weeks in adult and adolescent patients with moderate-to-severe atopic hand and foot dermatitis. The study met all pre-specified efficacy endpoints that assessed skin lesions and other domains of atopic hand and foot dermatitis. No specific safety concern arises from the safety data collected in adolescents. The safety data resulting from the study suggests that dupilumab is well tolerated in patients with hand and foot dermatitis and is overall consistent with the known safety profile in the AD study populations and AD patients. This information has been reflected in section 4.8, 5.1 and 5.2 of the SmPC. For more information, please refer to the Summary of Product Characteristics.

IB/0075	C.I.7.b - Deletion of - a strength	28/07/2023	19/04/2024	SmPC, Annex II, Labelling and PL	
II/0071	Update of section 4.8 of the SmPC in order to support the longer-term (5-year) safety of dupilumab in adults with moderate-to-severe Atopic Dermatitis (AD) based on final results from study R668-AD-1225 listed as a specific PASS category 3 study in the RMP. The study R668-AD-1225 was a phase 3, multicenter, open-label extension (OLE) study of dupilumab in adults with moderate-to-severe atopic dermatitis (AD) who had previously participated in dupilumab clinical trials. The main objective of this study is to assess the long-term safety of dupilumab administered in adult patients with AD. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/06/2023	19/04/2024	SmPC	Long term safety of dupilumab have been assessed in the open-label extension study R668-AD-1225 which enrolled adult study subjects with moderate-to-severe Atopic Dermatitis (AD) who had previously participated in controlled studies of dupilumab. The submitted results are consistent with the known safety profile in adults with moderate-to-severe AD. This information has been reflected in section 4.8 of the SmPC. For more information, please refer to the Summary of Product Characteristics.
IB/0073/G	This was an application for a group of variations. B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	26/05/2023	n/a		
II/0068	Update of sections 4.8 and 5.1 of the SmPC to	14/04/2023	19/04/2024	SmPC	Long term safety and efficacy of dupilumab have been

	include long-term safety and efficacy information in children based on final results from study LTS14424 - EXCURSION. This is an interventional one-year study, to evaluate the long-term safety and tolerability of dupilumab in children 6 to 11 years of age with asthma, who participated in a previous dupilumab asthma clinical study EFC14153. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				assessed in the open-label extension study EXCURSION in children 6 to 11 years of age with moderate-to-severe asthma who previously participated in the parent study VOYAGE. The submitted results are consistent with the efficacy and safety data results from the parent study. This information has been reflected in sections 4.8 and 5.1 of the SmPC. For more information, please refer to the Summary of Product Characteristics.
IB/0070/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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/04/2023	n/a		
II/0060	Extension of indication to include treatment of severe atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from Study R668-AD-1539; this is a phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 Months to <6 years with moderate-to-severe atopic dermatitis. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is	26/01/2023	15/03/2023	SmPC and PL	Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-0060'.

	updated in accordance. Version 9.0 of the RMP has also been approved. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). Amendments to the marketing authorisation In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended. Paediatric data Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0329/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, 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				
II/0069/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.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of	16/02/2023	n/a		

	an obsolete parameter) B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS				
IB/0066/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	27/01/2023	n/a		
II/0062	Extension of indication to include treatment of eosinophilic esophagitis (EoE) in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy, based on the pivotal Study R668-EE-1774. This is an ongoing phase 3, randomized, double-blind, placebo-controlled, 3-part (A, B, C) safety and efficacy study with an initial 24-week treatment period in adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with EoE, and which includes an extended treatment period to a total of 52 weeks. 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.	15/12/2022	23/01/2023	SmPC and PL	Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-0062'

	Version 8.2 of the RMP has also been approved. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). Amendments to the marketing authorisation In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended. Paediatric data Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0361/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. Similarity with authorised orphan medicinal products The CHMP by consensus is of the opinion that Dupixent is not similar to Jorveza within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
T/0067	Transfer of Marketing Authorisation	21/11/2022	16/12/2022	SmPC, Labelling and PL	
II/0063	Extension of indication to include treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy, based on results	10/11/2022	12/12/2022	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-63'

	from studies EFC16459 and EFC16460 (PRIME and PRIME2); these are two phase 3, 24-week, randomized, double-blind, placebo-controlled, multi-centre, parallel group studies undertaken to evaluate the efficacy and safety of dupilumab in patients 18 years of age and older with moderate to severe PN, who are inadequately controlled on topical prescription therapies or when those therapies are not advisable. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been approved. Furthermore, the PI is brought in line with the current excipients guideline. The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP). Amendments to the marketing authorisation In view of the data submitted with the variation, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended. Additional market protection Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix).				

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10645 /202203	Periodic Safety Update EU Single assessment - dupilumab	27/10/2022	n/a		PRAC Recommendation - maintenance
IB/0065/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation A.7 - Administrative change - Deletion of manufacturing sites	24/10/2022	n/a		
X/0057	Extension of application to register the new cell line "C3" and its associated "C3P1" manufacturing process for the production of dupilumab formulated active substance. Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure	21/07/2022	29/09/2022		
R/0053	Renewal of the marketing authorisation.	23/06/2022	02/09/2022	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Dupixent in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0059/G	This was an application for a group of variations. B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is	30/06/2022	29/09/2022	SmPC, Labelling and PL	

	an integrated part of the primary packaging B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging				
IB/0061/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	13/05/2022	02/09/2022	Annex II and PL	

X/0045/G	This was an application for a group of variations. Extension application to add a new strength of 100 mg solution for injection in pre-filled syringe with safety system (PFS-S) grouped with a type II variation (C.I.6.a) to include the treatment of asthma in children from 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment. As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.2 Rev1.The RMP has been amended (version 6.1). Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/01/2022	04/04/2022	SmPC, Labelling and PL	Refer to the scientific discussion: EMEA/H/C/004390/X/0045/G
II/0050/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.4.d - Change to in-process tests or limits	13/01/2022	n/a		

	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.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				
IB/0055/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.a.2.z - Changes in the manufacturing process of the AS - Other variation	20/12/2021	n/a		
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2021	04/04/2022	PL	
IAIN/0058	C.I.10 - Change in the frequency and/or date of submission of PSURs for human medicinal products	09/12/2021	04/04/2022	Annex II	
IB/0051/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	29/11/2021	n/a		

	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation				
PSUSA/10645 /202103	Periodic Safety Update EU Single assessment - dupilumab	11/11/2021	06/01/2022		Please refer to Dupixent - EMEA/H/C/PSUSA/00010645/202103 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0046	Update of section 4.8 to include a new ADR and review frequencies based on an updated safety review C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/09/2021	06/01/2022	SmPC and PL	Based on the cumulative review of cases of facial rash observed in clinical trial data, reported in post-marketing setting and in the literature, an association between dupilumab and the adverse effect of facial rash is considered a possibility. Therefore facial rash is added as new undesirable effect under section 4.8 of the SmPC with a frequency of uncommon based on pooled clinical trial data.
IB/0048/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	16/07/2021	n/a		

	Replacement/addition of a site where batch control/testing takes place B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation				
II/0044	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/06/2021	06/01/2022	SmPC	The submitted data of study AD1225 originate from a period between data cutoffs of 11 April 2016 and 01 December 2018 and include 1192 patients with a treatment exposure of ≥100 weeks, 357 patients with a treatment exposure duration of ≥148 weeks, and 139 patients with a treatment exposure duration of ≥156 weeks who had previously participated in controlled studies of dupilumab. No new safety concerns arise from the submitted data and their results suggest a continuously good tolerability. Overall cumulatively, in study (AD-1225), the long-term safety of repeat doses of dupilumab was assessed in 2,677 adults with moderate-to-severe AD exposed to 300 mg weekly dosing (99.7 %), including 347 who completed at least 148 weeks of the study. The long-term safety profile observed in this study up to 3 years was generally consistent with the safety profile of dupilumab observed in controlled studies.
II/0043/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	20/05/2021	n/a		

	which may have a significant impact on the medicinal product and is not related to a protocol 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				
II/0039	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/05/2021	06/01/2022	SmPC and PL	The MAH pooled several studies supporting the safety profile as defined in the initial Marketing authorisation and further variation applications for the indications currently approved. This included 12 completed randomized, placebo controlled clinical trials. These studies involved 4,206 patients receiving dupilumab and 2,326 patients receiving placebo during the placebo-controlled treatment period. The pooling of studies resulted in amendment and/or clarification of frequencies of several adverse drug reactions as follows: Injection site reactions (common), arthralgia (common) angioedema (uncommon); Blepharitis (uncommon); keratitis (uncommon); ulcerative keratitis (rare) ; anaphylactic reaction (are). Injection site reactions were grouped to include erythema, oedema, pruritus, swelling and pain. Headache was removed from the list of adverse drug reactions with appropriate justification. For more information, please refer to the Summary of Product Characteristics.
IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/05/2021	06/01/2022	SmPC, Labelling and PL	
PSUSA/10645 /202009	Periodic Safety Update EU Single assessment - dupilumab	06/05/2021	n/a		PRAC Recommendation - maintenance

IB/0042/G	This was an application for a group of variations. B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/02/2021	n/a		
II/0038/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 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.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.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	14/01/2021	n/a		

	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 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.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				
PSUSA/10645 /202003	Periodic Safety Update EU Single assessment - dupilumab	12/11/2020	11/01/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10645/202003.
IB/0040/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/01/2021	n/a		
IB/0037/G	This was an application for a group of variations. B.II.f.1.b.5 - Stability of FP - Extension of the shelf	22/12/2020	06/01/2022	SmPC	

	life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IB/0035/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation 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 B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	09/12/2020	06/01/2022	SmPC	
II/0027	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/10/2020	25/11/2020	SmPC and PL	Please refer to Scientific Discussion 'EMEA/H/C/004390/II/0027'.
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/2020	25/11/2020	PL	
II/0031/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	01/10/2020	n/a		

	of the AS 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.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				
II/0032	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2020	25/11/2020	SmPC	
PSUSA/10645 /201909	Periodic Safety Update EU Single assessment - dupilumab	30/04/2020	25/06/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10645/201909.
IAIN/0033	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	12/06/2020	n/a		
II/0030	Update of section 4.8 of the SmPC to include arthralgia as a new Adverse Drug Reaction (ADR) with a frequency not known. This is based on safety review of post-marketing data and PRAC recommendation adopted in the last PSUR assessment dated April 2020. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	14/05/2020	25/11/2020	SmPC and PL	Available data from the literature and reported post-marketing cases suggest evidence for a causal association between dupilumab exposure and 'Arthralgia', i.e. joint pain. Therefore, arthralgia is added as new ADR to section 4.8. of the SmPC with a frequency "unknown" based on post marketing data.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0029/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol	05/05/2020	n/a		
II/0024/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 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	17/04/2020	25/06/2020	Annex II	

	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.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
IB/0028	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	04/03/2020	n/a		
IB/0025/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	08/01/2020	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - 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 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				
IB/0023	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	20/12/2019	25/06/2020	SmPC	
IB/0022/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	21/11/2019	n/a		

	procedure				
PSUSA/10645 /201903	Periodic Safety Update EU Single assessment - dupilumab	31/10/2019	n/a		PRAC Recommendation - maintenance
II/0017	The application is for an extension of indication in patients with severe CRSwNP, who are As a consequence of this new indication on patients with CRSwNP, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to include pharmacological, efficacy and safety data. The Package Leaflet (PL) is updated accordingly. Additionally minor editorial QRD changes on excipients to the SmPC are introduced in section 6.6 in the 300mg and 200mg strength accordingly. Corresponding changes are implemented in the 200mg strength. Consequently the Annex IIIA is updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/09/2019	24/10/2019	SmPC and PL	Please refer to the assessment report.
II/0018/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a	17/10/2019	25/06/2020	SmPC, Annex II and Labelling	

	biol/immunol/immunochemical method B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IB/0021	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	20/08/2019	n/a		
II/0012	Extension of Indication for Dupixent to extend the atopic dermatitis indication to the paediatric adolescent population 12 years to 17 years. This is	27/06/2019	01/08/2019	SmPC and PL	Please refer to the variation assessment report.

	also submitted in accordance with the requirement of Article 46. 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 variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0019/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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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	10/07/2019	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0015	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	16/05/2019	01/08/2019	SmPC and PL	
X/0004/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/02/2019	06/05/2019	SmPC, Labelling and PL	
PSUSA/10645 /201809	Periodic Safety Update EU Single assessment - dupilumab	11/04/2019	n/a		PRAC Recommendation - maintenance
IA/0016	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)	29/03/2019	n/a		
II/0013/G	This was an application for a group of variations. 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	28/03/2019	n/a		

	processes 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 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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.z - Change in container closure system of the Finished Product - Other variation B.II.e.z - Change in container closure system of the Finished Product - Other variation B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant				

	impact on the delivery, use, safety or stability of the FP				
II/0009/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.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.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.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB 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 B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	17/01/2019	06/05/2019	Annex II	

	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				
II/0006/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.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 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.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.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	29/11/2018	06/05/2019	Annex II	

	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.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.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB				
PSUSA/10645 /201803	Periodic Safety Update EU Single assessment - dupilumab	04/10/2018	n/a		PRAC Recommendation - maintenance
IA/0011	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	01/10/2018	n/a		
IB/0010	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	07/09/2018	17/12/2018	SmPC	
IA/0007	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	14/06/2018	n/a		
II/0003/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of	25/05/2018	n/a		

	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.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				
II/0002	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	26/04/2018	n/a		
IB/0005	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	20/04/2018	n/a		
IB/0001	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	16/01/2018	17/12/2018	SmPC and PL	