RINVOQ

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/0027	Extension of indication to include treatment of moderately to severely active Crohn's disease in adult patients for RINVOQ, based on final results from three Phase III studies, two confirmatory placebo-controlled induction studies (Study M14 431/U-EXCEED/CD-1) and Study M14 433/U-EXCEL/CD-2) and a placebo-controlled maintenance/long-term extension study (Study M14-	23/02/2023	12/04/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Rinvoq EMEA/H/C/004760/II/0027'

[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).

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	430/U-ENDURE/CD-3). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC and the Annex II.D are updated. The Package Leaflet is updated in accordance. Version 13.3 of the RMP has been adopted. The MAH also took this opportunity to correct some figures in Section 5.3 of the SmPC. In addition, the MAH will make corrections to some of the translations as part of the linguistic review: the updates are generally either grammatical corrections, QRD alignments or correction to align with the EN text. The Romanian (RO), French(FR), Danish(DA), Italian(IT), Czech(CS), Polish(PL), Norwegian (NO), Portuguese (PT), Latvian(LV) and Bulgarian (BG) translations are affected. The variation leads to amendments to the Summary of Product Characteristics, Annex II 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				
PSUSA/10823 /202208	Periodic Safety Update EU Single assessment - upadacitinib	16/03/2023	n/a		PRAC Recommendation - maintenance
IB/0031	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	09/01/2023	n/a		

IA/0032	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/12/2022	n/a		
II/0020/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on 'Hypersensitivity' and to add 'serious hypersensitivity reactions' to the list of adverse drug reactions with the frequency "rare". The Package Leaflet has been updated accordingly. 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	10/11/2022	10/03/2023	SmPC and PL	Serious hypersensitivity reactions such as anaphylaxis and angioedema have been reported in patients receiving upadacitinib. If a clinically significant hypersensitivity reaction occurs, discontinue upadacitinib and institute appropriate therapy. For more information, please refer to the Summary of Product Characteristics.
II/0025/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.g.1.a - Introduction of a new design space or extension of an approved design space for the finished product - One or more unit operations in the manuf. process of the FP including the resulting IPCs and/or test procedures B.II.b.2.a - Change to importer, batch release	20/10/2022	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
IB/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/10/2022	n/a		
PSUSA/10823 /202202	Periodic Safety Update EU Single assessment - upadacitinib	29/09/2022	n/a		PRAC Recommendation - maintenance
IA/0029/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.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	19/09/2022	n/a		
IA/0028	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	25/08/2022	n/a		

II/0016	Extension of indication to include the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs), based on the final clinical study report from the pivotal study M19-944 Study 2 (nr-axSpA); a randomized, double-blind, phase III study evaluating the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with nr-axSpA who completed the double-blind period on study drug. As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated in accordance. A revised RMP version 8.0 is adopted. 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	23/06/2022	27/07/2022	SmPC and PL	Please refer to Scientific Discussion 'EMEA/H/C/004760/II/0016'
X/0012/G	This was an application for a group of variations. Extension application to add a new strength (45 mg) of the prolonged-release tablets, grouped with a type II variation (C.I.6.a) for the existing 15mg and 30mg strengths to include the treatment of adult patients with moderately to severely active ulcerative colitis	19/05/2022	22/07/2022	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion "Rinvoq EMEA/H/C/004760/X/0012/G".

	who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. As a consequence of the extension of indication sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC and the Additional risk minimisation measures in the Annex II are updated. The Package Leaflet is updated accordingly. The RMP (version 6.2) has been adopted. 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				
IB/0024/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.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	28/06/2022	n/a		
II/0015/G	This was an application for a group of variations. Grouping of 2 variations: C.I.4 - Update of sections 4.8 to add neutropenia	23/06/2022	27/07/2022	SmPC	The results of M19-944 Study 1 (SELECT AXIS 2) were submitted. This was a 14 week placebo controlled trial in 420 ankylosing spondylitis patients with prior exposure to bDMARDs. Long term (through week 104) data in AS patients who are

	and 5.1 of the SmPC in order to update efficacy information of Rinvoq in Ankylosing Spondylitis (AS) patients who are biologic DMARD inadequate responders (bDMARD-IR) based on interim results from study M19-944 Study 1; this is a Phase 3, randomized, double-blind, study evaluating the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with active AS who have an inadequate response (IR) to bDMARD. C.I.4 - Update of section 5.1 of the SmPC in order to include long term (through week 104) data in AS patients who are naïve to previous treatment with a bDMARD based on interim results from study M16-098; this is a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis; The RMP version 7.0 is adopted. In addition, the MAH took the opportunity to introduce minor editorial changes in the product information. 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				naïve to previous treatment with a bDMARD based on interim results from study M16-098 (SELECT AXIS 1) were also submitted. This was a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis. In both studies, a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14. A numerical difference between treatment groups was observed at from week 2 in SELECT AXIS 1 and week 4 in SELECT AXIS 2 (AS) for ASAS40 and response was maintained through week 64. In SELECT AXIS 1, efficacy was maintained through 2 years. The frequency of neutropaenia (2.8%) was added in the overall description of the most commonly reported adverse reactions in Section 4.8 of the SmPC. Neutropaenia is already list in the table of adverse reactions in this section of the SmPC. For more information, please refer to the Summary of Product Characteristics.

II/0019	Update of section 4.5 of the SmPC in order to add information about drug interaction with grapefruit as a CYP3A4 inhibitor based on literature references; 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	02/06/2022	27/07/2022	SmPC and PL	
IA/0023	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/05/2022	n/a		
IB/0021/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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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	06/05/2022	n/a		

II/0014	C.I.4 - Update of section 5.1 of the SmPC in order to update efficacy information based on interim results (Week 156) from studies M14-465 and M13-545; these are randomized phase 3, double blind studies to evaluate the long-term safety, tolerability and efficacy of upadacitinib in subjects with Rheumatoid Arthritis. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2022	22/07/2022	SmPC	Studies M14-465 and M13-545 are randomized phase 3, double blind studies evaluating the long-term safety, tolerability and efficacy of upadacitinib in subjects with Rheumatoid Arthritis. Section 5.1 of the SmPC has been updated with data on remission and low disease activity, ACR response, physical function response, and health related outcome measures through 3 years and radiographic response data through 2 years for patients who remained on their originally allocated treatment. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10823 /202108	Periodic Safety Update EU Single assessment - upadacitinib	24/03/2022	30/05/2022	SmPC and PL	Please refer to Rinvoq-EMEA/H/C/PSUSA/00010823/202108 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0018	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/03/2022	n/a		
PSUSA/10823 /202102	Periodic Safety Update EU Single assessment - upadacitinib	14/10/2021	16/12/2021	SmPC and PL	Please refer to Rinvoq-EMEA/H/C/PSUSA/00010823/202102 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0011	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	23/09/2021	n/a		

II/0009	C.I.4 - Update of sections 4.4 and 5.1 of the SmPC in order to amend the existing warning on vaccination based on the final results from vaccination substudy (within study M13-538) listed as a category 3 study in the RMP; this is an open-label extension to assess the impact of upadacitinib treatment with a stable background of methotrexate on immunological responses following administration of a pneumococcal vaccine in rheumatoid arthritis patients. The RMP version 5.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	16/12/2021	SmPC	A vaccination study was performed to assess the impact of upadacitinib treatment with a stable background of methotrexate on immunological responses following administration of a pneumococcal vaccine in rheumatoid arthritis patients who received either upadacitinib 15 mg QD or 30 mg QD. The primary endpoint of the substudy was the proportion of subjects with satisfactory humoral response to the inactivated pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) at Week 4. Satisfactory humoral response was defined as ≥ 2-fold increase in antibody concentration from the vaccination baseline in at least 6 out of the 12 pneumococcal antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). A total of 111 subjects received pneumococcal vaccination and at least 1 dose of upadacitinib after vaccination, of which 87 subjects received upadacitinib 15 mg and 24 subjects received upadacitinib 30 mg. A total of 108 (97.3%) subjects received concomitant MTX . A satisfactory humoral response was achieved by 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with upadacitinib 15 mg and 30 mg, respectively. SmPC new text Update of sections 4.4 to amend the information on vaccination with inactivated pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) in patients receiving upadacitinib concomitantly. Update of section 5.1 to reflect the final study results of the vaccination study. The influence of upadacitinib on the humoral response following the administration of

					inactivated pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) was evaluated in 111 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg (n=87) or 30 mg (n=24). 97% of patients (n=108) were on concomitant methotrexate. The primary endpoint was the proportion of patients with satisfactory humoral response defined as ≥ 2-fold increase in antibody concentration from baseline to Week 4 in at least 6 out of the 12 pneumococcal antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Results at Week 4 demonstrated a satisfactory humoral response in 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with upadacitinib 15 mg and 30 mg, respectively. For more information, please refer to the Summary of Product Characteristics.
X/0006/G	This was an application for a group of variations. Extension application to introduce a new strength (30 mg prolonged-release tablet), grouped with a type II variation (C.I.6.a) to add a new indication (treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy for Rinvoq). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3 of the SmPC, Annex II as well as the Package Leaflet are updated. The RMP (version 4.3) is adopted. Annex I_2.(c) Change or addition of a new strength/potency	24/06/2021	20/08/2021	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion EMEA/H/C/004760/X/0006/G

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10823 /202008	Periodic Safety Update EU Single assessment - upadacitinib	25/03/2021	21/05/2021	SmPC	Please refer to RINVOQ EMEA/H/C/PSUSA/00010823/202008 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0005	Extension of indication to include the treatment of active ankylosing spondylitis in adult patients for Rinvoq; 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. Minor editorial changes to the SmPC and Annex II are also agreed. Version 3.3 of the RMP has been adopted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	10/12/2020	22/01/2021	SmPC, Annex II and PL	Please refer to the scientific discussion: EMEA/H/C/004760/II/0005
II/0004	C.I.6 (Extension of indication) Extension of indication to include the treatment of active psoriatic arthritis in adult patients for Rinvoq; 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. Minor updates were made to the Annex II. Version 2.3 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	10/12/2020	22/01/2021	SmPC, Annex II and PL	Please refer to the Scientific Discussion: Rinvoq EMEA/H/C/4760/II/0004

	modification of an approved one				
IB/0008	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	13/11/2020	22/01/2021	SmPC	
PSUSA/10823 /202002	Periodic Safety Update EU Single assessment - upadacitinib	01/10/2020	n/a		PRAC Recommendation - maintenance
IB/0002	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/05/2020	n/a		
IA/0001	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	27/03/2020	22/01/2021	SmPC	