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/0056	Extension of indication to include the treatment of giant cell arteritis (GCA) in adult patients for RINVOQ based on final results from study M16-852. This is a phase 3, global, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of upadacitinib in subjects with GCA. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package	27/02/2025	04/04/2025	SmPC and PL	Please refer to Scientific Discussion 'EMEA/H/C/004760/II/0056'.

[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).

	Leaflet is updated in accordance. Version 16.0 of the RMP is agreed. 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				
II/0055	Update of sections 4.8 and 5.1 of the SmPC in order to include long term efficacy and safety data for ulcerative colitis based on results from study M14-533. This is a phase 3, multicentre, long-term extension study to evaluate the safety and efficacy of upadacitinib in subjects with ulcerative colitis. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/02/2025	04/04/2025	SmPC	The frequency of selected adverse reactions for ulcerative colitis in SmPC Section 4.8 are updated for infections, opportunistic infections (excluding tuberculosis) and laboratory abnormalities. The description of the selected adverse reactions is further updated to add information on gastrointestinal perforations: in the placebo-controlled maintenance period, gastrointestinal perforation was reported in 1 patient treated with placebo (1.5 per 100 patient-years) and no patients treated with upadacitinib 15 mg or 30 mg. In the long-term extension study, 1 patient treated with upadacitinib 15 mg (0.1 per 100 patient-years) and 1 patient treated with upadacitinib 30 mg (<0.1 per 100 patient-years) reported events. SmPC Section 5.1 on Ulcerative colitis is updated to include results of the long-term extension study, UC-4 (U-ACTIVATE): patients who achieved clinical remission in UC-3 per aMS at 1 year were eligible to continue with the same dose in the extension study (UC-4). At the entry of UC-4, there were 96 and 146 patients in clinical remission and 49 and 82 patients in endoscopic remission with upadacitinib 15 mg and 30 mg, respectively. This population is partly,

					but not fully, overlapping with the population presented in the above table depicting proportion of patients meeting endpoints at week 52 in the maintenance study UC 3. Among patients who achieved remission in UC-3 per aMS at 1 year and had available 96 weeks data, 55/70 (78.6%) and 75/89 (84.3%) maintained clinical remission and 22/34 (64.7%) and 40/54 (74.1%) maintained endoscopic remission after 96 weeks of additional treatment with upadacitinib 15 mg and 30 mg, respectively. In patients entering the extension study upon completion of UC-3 (1 year) and had available 96 weeks data, improvements in IBDQ total scores and in IBDQ domain scores were maintained through week 96 of UC-4. The safety profile of upadacitinib with long-term treatment was consistent with that in the placebo controlled period. For more information, please refer to the Summary of Product Characteristics.
II/0059	Update of section 4.4 of the SmPC in order to include a precaution regarding medication residue in stool based on post marketing data and literature. The Package Leaflet is updated accordingly. In addition, the MAH 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	12/12/2024	04/04/2025	SmPC and PL	Addition of the following warning on medication Residue in Stool in SmPC Section 4.4: reports of medication residue in stool or ostomy output have occurred in patients taking upadacitinib. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Patients should be instructed to contact their healthcare professional if medication residue is observed repeatedly. Patients should be clinically monitored, and alternative treatment should be considered if there is an inadequate therapeutic response. For more information, please refer to the Summary of Product Characteristics.

IB/0057/G	This was an application for a group of variations. 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 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	31/10/2024	n/a		
II/0052	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to change posology recommendations in adolescents with atopic dermatitis to include the 30mg dose option based on results from studies M16-045, M16-047 and M18-891 (pivotal phase 3 studies with adolescent substudies). The Package Leaflet is updated accordingly. The RMP version 14.0 is agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/09/2024	24/10/2024	SmPC and PL	Based on results from studies M16-045, M16-047 and M18-891 Section 4.2 of the SmPC is updated to reflect that in adolescents (12 to 17 years of age) weighing at least 30 kg, a dose of 15 mg is recommended. If the patient does not respond adequately to 15 mg once daily, the dose can be increased to 30 mg once daily. Efficacy results of the studies were reflected in section 5.1 of the SmPC. Section 4.8 of the SmPC is updated to reflect the studies results: a total of 541 adolescents aged 12 to 17 years with atopic dermatitis were treated in the global Phase 3 studies (n=343) and the supplemental adolescent substudies (n=198), of whom 264 were exposed to 15 mg and 265 were exposed to 30 mg. The safety profile for upadacitinib 15 mg and 30 mg in adolescents was similar to that in adults. With long-term exposure, the adverse drug reaction of skin papilloma was reported in 3.4% and 6.8% of adolescent patients with atopic dermatitis in the upadacitinib 15 mg and 30 mg groups, respectively. For more information, please refer to the Summary of

					Product Characteristics.
IA/0060	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/10/2024	n/a		
IB/0058/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue 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	07/10/2024	n/a		
R/0051	Renewal of the marketing authorisation.	25/07/2024	19/09/2024	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of RINVOQ in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10823 /202402	Periodic Safety Update EU Single assessment - upadacitinib	05/09/2024	n/a		PRAC Recommendation - maintenance

IB/0054	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	27/06/2024	n/a		
II/0050	Update of section 5.1 of the SmPC in order to include long term efficacy and safety information (up to week 104 data) from study M19-944 (Study 1); this is a phase 3 randomized, placebo-controlled, double-blind program to evaluate efficacy and safety of upadacitinib in adult subjects with axial spondyloarthritis followed by a remission-withdrawal period. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/06/2024	19/09/2024	SmPC	The long-term safety and efficacy data, up to week 104, of M19-994 study 1 (SELECT AXIS 2) was submitted. This was a 14-week placebo-controlled trial in 420 Ankylosing Spondylitis patients with prior exposure to bDMARDs. Subjects in the placebo group were switched to upadacitinib at Week 14, and maintenance of efficacy was evaluated in the Open-Label Extension Period through Week 104. Of the patients initially randomized and receiving upadacitinib, 163/211 (77.3%) completed the 104-week period. A total of 94 subjects who were randomized to the upadacitinib treatment group achieved ASAS40 response at Week 14. Out of these 94 subjects, 76 subjects (80.9%) achieved ASAS40 response at Week 104 based on NRI analysis. Therefore, the respective endpoints in section 5.1 of the SmPC are updated to highlight that the efficacy was maintained through 2 years. For more information, please refer to the Summary of Product Characteristics.
II/0049	Update of section 5.1 of the SmPC in order to include long term efficacy and safety information (up to week 104 data) from study SELECT-AXIS 2 (M19-944 (Study 2)); 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 nr-axSpA who completed the double-blind period on study drug. The MAH took also the opportunity to update the ATC code from L04AA44	13/06/2024	19/09/2024	SmPC	Of patients who were initially randomised to upadacitinib, 75% (117/156) in SELECT-AXIS 2 (nr-axSpA) continued therapy through 2 years. At week 52, around 63% (95% CI 55.2-70.4) of the upadacitinib treated subjects achieved an ASAS 40 response compared with around 43% (95% CI 34.9-50.4) in the placebo group. Efficacy was maintained through 2 years as assessed by the endpoints presented in the Table Clinical response in SELECT-AXIS 2 (nr-axSpA) of the

	into L04AF03. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				SmPC. Improvements in BASFI, total and nocturnal back pain, ASQoL and ASAS Health Index were maintained through 2 years. Improvement in inflammation as assessed by MRI was maintained through 2 years. The MAH took also the opportunity to update the ATC code from L04AA44 into L04AF03. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10823 /202308	Periodic Safety Update EU Single assessment - upadacitinib	21/03/2024	16/05/2024	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10823/202308.
II/0045	Submission of the final report from study M15-555, listed as a category 3 study in the RMP. This is phase 3, randomized, double-blind study comparing upadacitinib (ABT-494) monotherapy to methotrexate (MTX) in subjects with moderately to severely active rheumatoid arthritis with inadequate response to MTX. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/02/2024	n/a		Study M15-555 was a Phase 3 multicentre study that included 2 periods. Period 1 was a 14-week, randomized, double-blind, parallel-group, controlled period designed to compare the safety and efficacy of upadacitinib 30 mg once daily (QD) monotherapy and upadacitinib 15 mg QD monotherapy versus continuing MTX monotherapy for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). Period 2 was a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and upadacitinib 15 mg QD in subjects with RA who have completed Period 1. Following Protocol Amendment 5.0 approval, all subjects received open label upadacitinib 15 mg QD, including those on upadacitinib 30 mg QD. Prior to Protocol Amendment 5.0, all subjects in Period 2 were on upadacitinib with dose blinded. The CHMP concluded that no changes to the product information are required based on the long-term results from study M15-555. The study shows that efficacy of

					upadacitinib was clinically meaningful and well maintained over time in all treatment groups.
PSUSA/10823 /202302	Periodic Safety Update EU Single assessment - upadacitinib	12/10/2023	19/12/2023	SmPC and PL	Periodic Safety Update Report
IB/0048	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	12/12/2023	n/a		
IB/0043	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2023	n/a		
IA/0047	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	31/10/2023	n/a		
II/0042	Submission of the final report from study M13-545 listed as a category 3 study in the RMP (MEA/10). This is a Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/10/2023	n/a		Study M13-545 was a Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Once Daily Monotherapy to Methotrexate (MTX) Monotherapy in MTX-Naïve Subjects with Moderately to Severely Active Rheumatoid Arthritis (RA) which included two periods. Period 1 had two objectives. The first, was to compare the safety and efficacy of upadacitinib 7.5 mg QD monotherapy (for subjects in Japan only), 15 mg QD monotherapy, and 30 mg QD monotherapy versus weekly MTX monotherapy for the treatment of signs and symptoms of RA in MTX-naïve subjects with moderately to severely active RA. The second, was to compare the efficacy of upadacitinib 15 mg QD monotherapy and upadacitinib 30 mg QD monotherapy

					versus weekly MTX monotherapy for prevention of structural progression in MTX-naïve subjects with moderately to severely active RA. The objective of Period 2 was to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD (for subjects in Japan only), 15 mg QD, and 30 mg QD in subjects with RA who have completed Period 1. Following a protocol amendment, subjects who previously received blinded upadacitinib 15 mg and 30 mg QD were switched to open-label upadacitinib 15 mg QD. Subjects who previously received blinded MTX received open-label MTX. The CHMP concluded that no changes to the product information are required based on the long-term results from study M13-545. The efficacy results remained stable and there were no new safety concerns.
IB/0044/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	06/10/2023	n/a		

	variation 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.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				
II/0035	Submission of the final report from study M13-549 listed as a category 3 study in the RMP. This is a Phase III, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2023	n/a		Study M13-549 was a Phase 3 multicenter study that included two periods. Period 1 (results submitted with the initial marketing authorisation application) was a 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg once daily (QD) and upadacitinib 30 mg QD vs. placebo. Subjects who completed the Week 12 visit (end of Period 1) entered the blinded long-term extension portion of the study, Period 2 (up to 5 years). Subjects who were assigned to upadacitinib treatment groups continued to receive upadacitinib 15 mg QD or upadacitinib 30 mg QD per original randomization assignment in a blinded manner and subjects who were assigned to placebo were switched to receive upadacitinib 15 mg QD or upadacitinib 30 mg QD in a blinded fashion per pre- specified randomization assignments. Following a protocol amendment, all subjects received open label upadacitinib 15 mg QD, including those on upadacitinib 30 mg QD, with the earliest switch occurring at the Week 168 visit, before that all doses were blinded.

					The CHMP concluded that no changes to the product information or the risk management plan are required based on the long-term results from study M13-549. The efficacy results remained stable and there were no new safety concerns.
II/0034	Submission of the final report from study M13-542, listed as a category 3 study in the RMP. This is a phase 3, randomized, double-blind study comparing upadacitinib (ABT-494) to placebo on stable conventional synthetic disease-modifying anti rheumatic drugs (csDMARDs) in subjects with moderately to severely active rheumatoid arthritis with inadequate response or intolerance to biologic DMARDs (bDMARDs). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2023	n/a		Study M13-542 was a Phase 3 multicenter study that included 2 periods. Period 1 (results submitted with the initial marketing authorization application) was a 24-week, randomized, double-blind, parallel-group period (placebo-controlled for the first 12 weeks), designed to compare the safety and efficacy of upadacitinib 30 mg once daily (QD) and upadacitinib 15 mg QD vs. placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD. Period 2 was a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and upadacitinib 15 mg QD in subjects with RA who had completed Period 1. Following Protocol Amendment 4.0 approval, all subjects received open-label upadacitinib 15 mg QD, including those who had previously been on upadacitinib 30 mg QD, with the earliest switch occurring at the Week 180 visit. The CHMP concluded that no changes to the product information and the risk management plan are required based on the long-term results from study M13-542. The efficacy results remained stable and there were no new safety concerns.
IA/0041	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	16/08/2023	n/a		

	product formulation - Change that does not affect the product information				
II/0038	Update of sections 4.4 and 5.1 of the SmPC in order to include results from a sub-study of Study M14-465. The objective of the sub-study was to assess the immunogenicity of the adjuvanted recombinant glycoprotein E herpes zoster vaccine in rheumatoid arthritis subjects receiving upadacitinib 15 mg once daily (QD) with background MTX. In addition, the MAH is taking this opportunity to correct translation errors in Section 4.4 of the Dutch, Finnish, French, German, Hungarian, Italian, Latvian, Lithuanian, Norwegian, Polish, Portuguese, Romanian, Slovakian, Slovenian and Spanish product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2023	19/12/2023	SmPC	Concomitant use of adjuvanted recombinant glycoprotein E herpes zoster vaccine with upadacitinib was studied in sub-study M14-465 and its results are included in the SmPC for Rinvoq as follows: “The influence of upadacitinib on the humoral response following administration of adjuvanted recombinant glycoprotein E herpes zoster vaccine was evaluated in 93 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg. 98% of patients were on concomitant methotrexate. 49% of patients were on oral corticosteroids at baseline. The primary endpoint was the proportion of patients with a satisfactory humoral response defined as ≥ 4 fold increase in pre-vaccination concentration of anti-glycoprotein E titer levels at week 16 (4 weeks post-dose 2 vaccination). Vaccination of patients treated with upadacitinib 15 mg resulted in a satisfactory humoral response in 79/90 (88% [95% CI: 81.0, 94.5]) of patients at week 16.” Prior to initiating upadacitinib treatment, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines. For more information, please refer to the Summary of Product Characteristics.
IB/0040/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or	14/07/2023	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.1.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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0039	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	16/06/2023	n/a		
IB/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/06/2023	n/a		
II/0033	Submission of the final report from study M16-098 listed as a category 3 study in the RMP. This is a multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of	12/05/2023	n/a		This is the final report for study M016-098 “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis” listed as a

	upadacitinib in subjects with active ankylosing spondylitis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				category 3 study in the RMP. The long-term safety results in this final dataset from study M16-098 are consistent with results reported in the 1-year and 2-year interim reports assessed as part of variations EMEA/H/C/004760/II/0005 and EMEA/H/C/004760/II/0015/G. No new safety signals have been identified in this final report. No update of the SmPC has been proposed by the MAH with this application; this is endorsed by the CHMP.
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 M14-430/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	23/02/2023	12/04/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Rinvoq EMEA/H/C/004760/II/0027'

	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
A20/0017	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 28 January 2022 the opinion of the European Medicines Agency further to the safety issues on MACE, VTE, serious infections, malignancy and mortality for all JAK inhibitors used in the treatment of inflammatory disorders. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion was adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.	23/01/2023	10/03/2023	SmPC, Annex II and PL	Please refer to the assessment report: Rinvoq (upadacitinib) EMEA/H-A20/1517/C/004760/0017

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	20/10/2022	n/a		

	manuf. process of the FP including the resulting IPCs and/or test procedures 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.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	25/08/2022	n/a		

	size				
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	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".

	with moderately to severely active ulcerative colitis 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	