EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Xeljanz

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
IAIN/0058	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	06/12/2023		Annex II and PL	
II/0053/G	This was an application for a group of variations.	30/11/2023	n/a		

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

	B.II.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.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes				
IA/0057	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)	03/11/2023	n/a		
II/0054	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/10/2023	n/a		
IB/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2023		SmPC and PL	
II/0052	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/08/2023	n/a		

IA/0055	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	10/07/2023	n/a		
PSUSA/10588 /202211	Periodic Safety Update EU Single assessment - tofacitinib	08/06/2023	n/a		PRAC Recommendation - maintenance
A20/0048	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: Xeljanz (tofacitinib) EMEA/H-A20/1517/C/004214/0048
IA/0050	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	09/11/2022	n/a		

PSUSA/10588/202111	Periodic Safety Update EU Single assessment - tofacitinib	23/06/2022	13/09/2022	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10588/202111.
IA/0049	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	23/08/2022	n/a		
II/0039	Extension of indication to include treatment of active ankylosing spondylitis for Xeljanz prolonged release tablets; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, editorial changes have been introduced throughout the PI. The Package Leaflet is updated in accordance. Version 28.1 of the RMP has also been submitted. 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	19/05/2022	24/06/2022	SmPC and PL	Please refer to Scientific Discussion 'Xeljanz-H-C-004214-II-0039'
II/0044	C.I.3.b - Update of section 4.4, 4.8 and 5.1 to add warnings and safety data on serious infections, viral reactivation, non-melanoma skin cancer and fractures. This is based on the final results from study A3921133 listed as a category 3 study in the RMP; this is a post-authorisation safety study conducted to evaluate the safety of tofacitinib 5mg and 10 mg compared to TNFi in adults' subjects aged	10/06/2022	13/09/2022	SmPC, Labelling and PL	SmPC new text Section 4.4 Fractures have been observed in patients treated with tofacitinib. Tofacitinib should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage.

	≥50 years with moderately or severely active RA and with at least 1 additional CV risk factor. The Package Leaflet is updated accordingly. The RMP version 21.1 has also been submitted. In addition, the MAH took the opportunity to update the Outer carton (section 4 for oral solution) to include a total volume of 240 mL as requested following the completion of the procedure EMEA/H/C/004214/X/0024/G. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				Section 4.8 Viral reactivation In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) for herpes zoster for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), and 1.18 (0.90, 1.52) patients with events per 100 patient-years, respectively. Laboratory tests […]ALT elevations greater than or equal to 3x ULN were observed in 6.01%, 6.54% and 3.77% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively. AST elevations greater than or equal to 3x ULN were observed in 3.21%, 4.57% and 2.38% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively. […]changes in lipid parameters from baseline through 24 months are summarised below: • Mean LDL cholesterol increased by 13.80%, 17.04%, and 5.50% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 12.71%, 18.14%, and 3.64%, respectively, • Mean HDL cholesterol increased by 11.71%, 13.63%, and 2.82% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was

					11.58%, 13.54%, and 1.42%, respectively For more information, please refer to the Summary of Product Characteristics.
II/0046	Update of section 5.3 of the SmPC in order to update safety information on reproductive and developmental toxicity based on final study results from An Oral (Gavage) Juvenile Toxicity Study of CP-690,550 in Sprague Dawley Rats (MEA 022) listed as a cat 3 study in the RMP. The RMP version 26.1 has also been updated. In addition, MAH is also taking this opportunity to update the contact details of the 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	07/04/2022	24/06/2022	SmPC and PL	Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility (decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions), parturition, and peri/postnatal development. Tofacitinib had no effects on male fertility, sperm motility or sperm concentration. Tofacitinib was secreted in milk of lactating rats at concentrations approximately 2-fold those in serum from 1 to 8 hours postdose. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans.
R/0040	Renewal of the marketing authorisation.	16/12/2021	04/03/2022	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Xeljanz in the approved indications remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: • Important safety issues have been identified: Signal of increased all-cause mortality identified by the MAH in completed study A3921133 (which is classified as "closed" by the MAH for the purposes of the renewal). The MAH reopened the signal "all-cause mortality" after completion of the clinical study A3921133. However, based on the information provided (a short summary of MAH's

					assessment of their reopened signal) no final conclusions can be drawn by the PRAC on the signal of all-cause mortality as not all data of the completed study have been provided. The PRAC does not support the MAH's conclusion that the signal of all-cause mortality can be refuted. The final study report was expected to be submitted for assessment in August 2021, however the MAH did not submit this yet and therefore has classified the A3921133 study as on-going for the purposes of this renewal. Complete data on the final study results are necessary for proper assessment. With submission of the final study report, KM curves for all-cause mortality, CV death and death associated with infections should be also provided. Further, a tabulated list of individual causes of death (e.g. CV mortality should be further specified) should be also provided as well as assessment of possible risk factors for death. The final study report of study A3921133 is awaited and once available, the results will then be further assessed. No further action within the scope of the renewal is required. The conclusions of the renewal procedure are without prejudice to the conclusions of the ongoing assessment of the final study report of study A3921133.
IB/0045	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/01/2022	n/a		
II/0035	Extension of indication to include treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy for XELJANZ film-coated tablets; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the	14/10/2021	15/11/2021	SmPC and PL	Please refer to Scientific Discussion Xeljanz-H-C-4214-II-35

	SmPC are updated. The Package Leaflet is updated in accordance. Version 17.1 of the RMP has been accepted. 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/0042/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/11/2021	04/03/2022	Annex II	
IB/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2021	15/11/2021	SmPC and PL	
II/0028	Update of section 4.4 of the SmPC and annex IID of the product information based on the submission of the final report on Biospecimen testing study, listed as a category 3 study in the RMP. This is an exploratory study to assess biomarkers related to VTE events in Study A3921133. The RMP version 14.4 has also been submitted. The requested variation proposed amendments to	02/09/2021	15/11/2021	SmPC and Annex II	In the randomised post authorisation safety study A3921133 in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors. In the post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in

	the Summary of Product Characteristics, Package Leaflet to the Risk Management Plan (RMP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× ULN versus those with D-dimer level <2× ULN; this was not evident in TNF inhibitor treated patients. Interpretation is limited by the low number of VTE events and restricted D dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D Dimer testing in this study. Therefore, for patients with RA with known risk factors for VTE, it is recommended to consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN and confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib. Information on VTE in the Guide for Healthcare professional, and prescriber treatment maintenance checklist have also been updated in addition to the prescribing information to include information regarding testing D-dimer levels after approximately 12 months of treatment in patients with RA with known risk factors for VTE. This is reflected in annex IID of the product information.
IAIN/0041	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/08/2021	15/11/2021	SmPC and PL	

X/0024/G	This was an application for a group of variations. Extension application to introduce a new pharmaceutical form (oral solution, 1mg/ml) grouped with a type II variation (C.I.6.a) to add a new indication (treatment of active polyarticular course juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older). The RMP (version 12.1) is updated in accordance. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/06/2021	18/08/2021	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion: EMEA/H/C/004214/X/0024/G
II/0027	Update of sections 4.1, 4.2, 4.4 , 4.8, 5.1 and 5.2 of Xeljanz 11mg prolonged-release tablets SmPC in order to include the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease modifying antirheumatic drug therapy; as an alternative to the immediate release film-coated tablets; Section 4.2 of Xeljanz film-coated tablets is also updated to include switching with the prolonged-release tablet in the treatment of PsA. The Package Leaflet is updated accordingly. The RMP version 13.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	24/06/2021	23/07/2021	SmPC and PL	The extension of the prolonged-release (PR) posology to the treatment of PsA patients was based on extrapolation from the immediate release (IR) formulation data by means of an exposure-response (E/R) based bridging approach, given that the efficacy of the prolonged release formulation was previously established as similar to that of IR in RA patients, using both interventional and non-interventional data. Based on the demonstrated bioequivalence between PR and IR formulations in terms of AUC and Cmax, and considering the 29% lower Cmin for PR 11 mg QD compared to IR 5 mg BID, the fluctuation in exposure with the PR formulation has no impact on the efficacy that is substantially driven by the overall exposure expressed in terms of AUC or Cavg. The Longitudinal E/R analysis confirmed that although

	data				Cmin, Cmax and Cavg have a similar impact in terms of predictability of a clinical response, both in PsA and PsO patients, Cmin has a lower ability to predict efficacy. Moreover, as already demonstrated in RA patients, the onset of clinical response in PsA patients in terms of ACR 20, 50 and 70 needs a longer time period (10-13 weeks for ACR20/50 and 15-19 weeks for ACR70) than time to reach steady-state (5-10 days), confirming that the efficacy outcome depends on the maintained exposure over time. Overall, the data presented demonstrated that 11 mg prolonged-release formulation once a day can be used in PsA patients. No new safety signals emerged from the submitted analysis: a comparison between PsA and RA patients who were treated with the IR formulation (5 and 10 mg BID) across the different clinical trials. The safety profile seems to be consistent between RA and PsA indications, with even a tendency towards more unfavourable effects of treatment in the RA population regardless of the formulations, likely attributable to the nature of disease and longer drug exposure. However, the increased incidence of serious infections noted in the Corrona registry with the PR formulation was noted and reflected in Section 4.8 of the SmPC as follows: Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher incidence rate of serious infection was observed for the 11 mg prolonged-release tablet administered once daily than the 5 mg film-coated tablet administered twice daily. Crude incidence rates (95% CI) (i.e., not adjusted for age or sex) from availability of each formulation at 12 months following initiation of treatment

					were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the 11 mg prolonged-release tablet once daily and 5 mg film-coated tablet twice daily groups, respectively. The unadjusted hazard ratio was 1.30 (95% CI: 0.67, 2.50) at 12 months and 1.93 (95% CI: 1.15, 3.24) at 36 months for the 11 mg prolonged-release once daily dose compared to the 5 mg film-coated twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time.
PSUSA/10588 /202011	Periodic Safety Update EU Single assessment - tofacitinib	10/06/2021	n/a		PRAC Recommendation - maintenance
II/0038	Submission of an updated RMP version 17.1 in order to incorporate the Category 3 US-based drug utilisation study A3921348 into the Category 3 protocol of the US-based active surveillance study A3921347. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	06/05/2021	n/a		Study A3921347, a prospective non-interventional active surveillance study in the US, to quantify the incidence of key safety events of interest in moderate-to-severe UC patients treated with tofacitinib and other systemic therapies in the real world setting, and Study A3921348, a US-based drug utilization study using either Electronic Health Records or administrative claims database, are Category 3 in the EU RMP. Both studies are combined to allow for the consolidation of resources.
IB/0036/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	06/05/2021	n/a		

	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				
IB/0031	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)	14/01/2021	23/07/2021	SmPC and PL	
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/11/2020	23/07/2021	PL	
IB/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2020	23/07/2021	SmPC, Labelling and PL	
II/0023	Submission of the final report from Study A3921205 listed as a category 3 study in the RMP. This is an Observational, Post-Authorization Safety Study (PASS) within the Consortium of Rheumatology Researchers of North America (CORRONA) Registry Comparing Rates of Malignancy, Cardiovascular and Serious Infection Outcomes among Patients Treated for Moderately to Severely Active Rheumatoid Arthritis. The RMP version 10.1 has been adopted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/10/2020	n/a		The MAH submitted the final study report of the category 3 PASS US Corrona RA Registry. This observational study conducted in the US, included patients with RA and compared the safety of tofacitinib with bDMARDs. Based on the result of this study no update to the product information was required. In RMP version 10.1 the information regarding category 3 PASS US Corrona RA Registry has been updated to reflect that this study has been completed. All corresponding sections of the RMP have been updated accordingly.
IB/0026/G	This was an application for a group of variations.	29/09/2020	23/07/2021	SmPC	

	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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.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.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.II.a.z - Change in description and composition of the Finished Product - Other variation				
II/0025	To submit the final report from Study A3921092, a long term, open-label extension study of tofacitinib for the treatment of adult patients with psoriatic arthritis (PsA), listed as a category 3 study in the RMP. An updated RMP version 11.1 has also been	03/09/2020	n/a		The study results showed that overall adverse events, venous thromboembolism, malignancy, major adverse cardiac events, hepatic events, and laboratory abnormality incidences were consistent with rates found for tofacitinib-treated rheumatoid arthritis (RA) subjects. As expected,

	submitted. The MAH took also the opportunity to update the milestones for study A3921347 (US UC active surveillance study) in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				tofacitinib 10 mg BID ("bis in die" twice a day) dose showed worse safety profile than to the 5 mg BID dose. Mortality rate was low and no death event was judged by the investigator to be associated with tofacitinib. Tofacitinib's safety profile in PsA subjects was consistent with that of RA subjects, with slightly lower rates in the PsA dataset possibly related to shorter tofacitinib exposure in this setting. Overall, no new safety signals were observed. Tofacitinib's safety profile is adequately reflected and risks can be mitigated or managed as described in the SmPC and RMP. Data support long term 5 mg BID tofacitinib use for PsA treatment in adult subjects and are appropriately reflected in the current version of the SmPC.
PSUSA/10588 /201911	Periodic Safety Update EU Single assessment - tofacitinib	11/06/2020	n/a		PRAC Recommendation - maintenance
IB/0022	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/04/2020	n/a		
IB/0021	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/03/2020	n/a		
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/03/2020	n/a		
A20/0017	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 May 2019 the opinion of the European Medicines	14/11/2019	31/01/2020	SmPC, Annex II and PL	Please refer to the assessment report: Xeljanz - EMEA/H/A-20/1485/C/4214/0017

	Agency further to a potential increased risk of pulmonary embolism and overall mortality associated with the use of Xeljanz. The CHMP was requested to assess the impact thereof on the benefit-risk balance of 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 should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.				
IB/0018	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	19/12/2019	n/a		
X/0012	Extension application to introduce a new pharmaceutical form (prolonged-release tablet) associated with a new strength (11 mg), and presented in pack sizes of 28, 30, 90 and 91 tablets. An updated RMP (version 6.1) has been adopted. Annex I_2.(b) Change of pharmacokinetics change in rate of release Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	17/10/2019	16/12/2019	SmPC, Annex II, Labelling and PL	

PSUSA/10588/201811	Periodic Safety Update EU Single assessment - tofacitinib	16/05/2019	n/a		PRAC Recommendation - maintenance
PSUSA/10588/201805	Periodic Safety Update EU Single assessment - tofacitinib	29/11/2018	n/a		PRAC Recommendation - maintenance
T/0015	Transfer of Marketing Authorisation	26/09/2018	08/11/2018	SmPC, Labelling and PL	
IAIN/0014	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	07/09/2018	08/11/2018	SmPC, Labelling and PL	
X/0005/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	31/05/2018	26/07/2018	SmPC, Annex II, Labelling and PL	
II/0006	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/04/2018	25/06/2018	SmPC, Annex II and PL	
II/0008	Update of sections 4.4, and 5.1 of the SmPC to add a warning regarding the increased risk of infection when corticosteroids are used concomitantly and to reflect information from study A3921187 (ORAL	14/06/2018	08/11/2018	SmPC and PL	Over the course of ORAL Strategy, responses with tofacitinib 5 mg twice daily + MTX were numerically similar compared to adalimumab 40 mg + MTX and both were numerically higher than tofacitinib 5 mg twice daily. Please

	Strategy), respectively; this is a phase 3b/4 randomised, double-blind study of 5 mg of Tofacitinib with and without methotrexate in comparison to adalimumab with methotrexate in subjects with moderately to severely active rheumatoid arthritis. The Package Leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				refer to the Summary of Product Characteristics for more information from the ORAL Strategy study. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in RA patients receiving XELJANZ. Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection.
PSUSA/10588 /201711	Periodic Safety Update EU Single assessment - tofacitinib	17/05/2018	n/a		PRAC Recommendation - maintenance
II/0010	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/04/2018	25/06/2018	SmPC and PL	
II/0009	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/04/2018	n/a		
II/0003	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/12/2017	21/06/2018	SmPC	
PSUSA/10588 /201705	Periodic Safety Update EU Single assessment - tofacitinib	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0001	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	24/05/2017	21/06/2018	SmPC, Labelling and	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes			PL	