Jakavi

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/0068	Update of section 4.4 of the SmPC in order to add new warnings on 'Major adverse cardiac events (MACE)', 'Thrombosis', and 'Second primary malignancies', following an Art. 20 Class Referral involving JAK inhibitors approved to treat rheumatoid arthritis. The PIL is updated accordingly. C.I.1.c - Change(s) in the SPC, Labelling or PL	21/03/2024		SmPC and PL	SmPC new text Major adverse cardiac events (MACE) In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non fatal myocardial infarction (MI)

[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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	intended to implement the outcome of a Union referral procedure - The product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH				and non-fatal stroke, was observed with tofacitinib compared to tumour necrosis factor (TNF) inhibitors. MACE have been reported in patients receiving Jakavi. Prior to initiating or continuing therapy with Jakavi, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older, patients who are current or past long time smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors. Thrombosis In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of venous thromboembolic events (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors. Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Jakavi. In patients with MF and PV treated with Jakavi in clinical studies, the rates of thromboembolic events were similar in Jakavi and control-treated patients. Prior to initiating or continuing therapy with Jakavi, the benefits and risks for the individual patient should be considered, particularly in patients with cardiovascular risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)”).

					Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. Second primary malignancies In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma, and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors. Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Jakavi. Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of the MF and PV patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. For more information, please refer to the Summary of Product Characteristics.
IAIN/0072	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	13/03/2024	n/a		

IAIN/0071/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of manufacturing sites	21/12/2023	n/a		
PSUSA/10015 /202302	Periodic Safety Update EU Single assessment - ruxolitinib	28/09/2023	n/a		PRAC Recommendation - maintenance
IA/0069/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites	21/09/2023	n/a		
IA/0067	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	17/07/2023	n/a		
IA/0065/G	This was an application for a group of variations. 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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	23/03/2023	n/a		

	in the manufacturing process				
IA/0064	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	25/01/2023	n/a		
IB/0063	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/01/2023	n/a		
IA/0062	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	14/10/2022	n/a		
PSUSA/10015 /202202	Periodic Safety Update EU Single assessment - ruxolitinib	29/09/2022	n/a		PRAC Recommendation - maintenance
II/0053	Extension of indication to include treatment of patients with acute and chronic GvHD aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies for Jakavi; 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. Version 14.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representative for The Netherlands in the Package Leaflet.	24/03/2022	29/04/2022	SmPC and PL	Please refer to Scientific Discussion 'Jakavi-H-C-2464-II-0053'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0060	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	21/04/2022	n/a		
IA/0059	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	19/04/2022	n/a		
II/0057/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant	28/10/2021	n/a		

	update to the relevant AS section in the dossier 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.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
PSUSA/10015 /202102	Periodic Safety Update EU Single assessment - ruxolitinib	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0058	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	31/08/2021	29/04/2022	SmPC and PL	
II/0050	Update of section 4.2 and 5.1 of the SmPC in order to update the posology and the method of administration as well as to include information on the A2201/EXPAND study CINC424A2201. The changes are based on final results of a Category 3	24/06/2021	28/07/2021	SmPC and PL	The recommended starting dose for patients with a platelet count between 75,000 to less than 100,000/mm3 is 10 mg orally twice daily and the recommended starting dose for patients with platelet count between 50,000 to less than 75,000/mm3 is to 5 mg orally twice daily.

	clinical study, phase Ib to fulfill an RMP post approval commitment. This is a dose-finding study intended to establish the maximum safe starting dose (MSSD) of ruxolitinib tablets administered orally to patients with myelofibrosis (MF) in the previous unstudied population of patients who had baseline platelet counts between ≥50×109/L and <100×109/L. The Package Leaflet is updated accordingly. The RMP (final version 12.1) has also been submitted including, as well, the review of safety concerns in compliance with the Good Pharmacovigilance Practices Module V, Revision 2, as well as recent PRAC outcome on PSUR (Procedure no.: EMEA/H/C/PSUSA/00010015/202002, CHMP Opinion dated 15-Oct-2020). The MAH also took the occasion to include some editorial changes in the text. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Dose reductions should be considered if the platelet count decreases during treatment as outlined in the Summary of medicinal product characteristics (SmPC) table 2. For more information, please refer to the Summary of Product Characteristics.
IAIN/0056	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	17/06/2021	28/07/2021	Annex II and PL	
IA/0054	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	12/03/2021	n/a		

PSUSA/10015 /202002	Periodic Safety Update EU Single assessment - ruxolitinib	15/10/2020	14/12/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10015/202002.
IA/0051	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	09/12/2020	n/a		
IB/0049	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/10/2020	28/07/2021	SmPC, Annex II, Labelling and PL	
II/0044	Update of the SmPC sections 5.1 and 4.8 with efficacy and safety information to reflect the 5-year follow-up data from the B2301 Week 256 final clinical study report (CSR). The PL was updated accordingly. The final analyses presented in the CSR are submitted to fulfil the Post-Authorisation Measure, therefore the Annex II.D of the Product Information is updated accordingly. The changes have been reflected in the RMP version 11 submitted withe the procedure II/43. The requested variation proposed amendments to the product information, Summary of Product Characteristics and Annex II. The PL was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	11/06/2020	14/12/2020	SmPC, Annex II and PL	The MAH submitted a final 5-year clinical study report for the REPONSE study (B2301) to analyse long term efficacy and safety up to 256 week of treatment with Jakavi. As expected, Adverse Events (AEs) frequencies have increased with prolonged exposure during the course of the study. The changes observed suggest a stable safety profile during prolonged treatment and they are reflected in the revised product information and RMP. Apart from ADR frequencies under long-term ruxolitinib treatment, this post-authorisation study specifically addressed haematological transformation, non-melanoma skin-cancer and second malignancies. Non-melanoma skin cancers constitute the most frequently occurring second malignancies observed and is listed as an Important potential risk in the RMP. The SmPC has been updated with the relevant updated ADR frequencies in section 4.8. Pneumonia was less

	new quality, preclinical, clinical or pharmacovigilance data				common for ruxolitinib compared with BAT therapy but was still considered an ADR also for MF, similar to PV, and has been included in the SmPC 4.8. A tabular presentation of efficacy data over time has been provided in section 5.1 of the SmPC.
II/0043	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/03/2020	09/06/2020	SmPC	
IAIN/0047	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	09/01/2020	09/06/2020	Annex II and PL	
IA/0046/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/12/2019	n/a		

IA/0045/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	23/10/2019	n/a		
PSUSA/10015 /201902	Periodic Safety Update EU Single assessment - ruxolitinib	05/09/2019	n/a		PRAC Recommendation - maintenance
II/0041	Update of section 4.5 of the SmPC based on the final results of a Drug-Drug Interaction (DDI) study INC4242A2106, fulfilling a Post-Authorisation Measure (MEA 0016) requested as part of a previous type II variation (Procedure No. EMEA/H/C/002464/II/0025). The study INC4242A2106 evaluated the effect of multiple doses of fluconazole on the pharmacokinetics of ruxolitinib administered as a single dose in an open-label, crossover study in healthy subjects. An updated RMP version 10 was submitted accordingly. Furthermore, the RMP template was adapted to revision 2 in line with GVP Module V Rev.2 (EMA/838713/2011 Rev 2). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/05/2019	09/06/2020	SmPC	In healthy subjects co administration of ruxolitinib (10 mg single dose) with a dual CYP2C9 and CYP3A4 inhibitor, fluconazole, resulted in ruxolitinib Cmax and AUC that were higher by 47% and 232%, respectively, than with ruxolitinib alone.
II/0040	Update of section 5.3 of the SmPC based on final	16/05/2019	09/06/2020	SmPC	In juvenile rat studies, administration of ruxolitinib resulted

	results from studies from the juvenile toxicity studies 1570143 (dose range finding juvenile study) and 157014 (juvenile development study). An updated RMP version 10 was submitted accordingly. The RMP was also updated in line with the template of the GVP Module V Rev.2 (EMA/838713/2011 Rev 2). Finally, the RMP changes requested by the PRAC in the latest PSUR (PSUSA-10015-201802) have been also implemented in this RMP. In addition, the MAH has taken the opportunity to align this RMP to the revised RMP template and to the GVP Module V Rev.2 (EMA/838713/2011 Rev 2). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				in effects on growth and bone measures. Reduced bone growth was observed at doses ≥5 mg/kg/day when treatment started on postnatal day 7 (comparable to human newborn) and at ≥15 mg/kg/day when treatment started on postnatal days 14 or 21 (comparable to human infant, 1–3 years). Fractures and early termination of rats were observed at doses ≥30 mg/kg/day when treatment was started on postnatal day 7. Based on unbound AUC, the exposure at the NOAEL (no observed adverse effect level) in juvenile rats treated as early as postnatal day 7 was 0.3 fold that of adult patients at 25 mg twice daily, while reduced bone growth and fractures occurred at exposures that were 1.5- and 13-fold that of adult patients at 25 mg twice daily, respectively. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than bone development, the effects of ruxolitinib in juvenile rats were similar to those in adult rats. Juvenile rats are more sensitive than adult rats to ruxolitinib toxicity.
IA/0039/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	18/02/2019	n/a		
PSUSA/10015 /201802	Periodic Safety Update EU Single assessment - ruxolitinib	06/09/2018	n/a		PRAC Recommendation - maintenance
IG/0950	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	18/06/2018	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
T/0035	Transfer of Marketing Authorisation	26/03/2018	22/05/2018	SmPC, Labelling and PL	
IAIN/0036	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	24/04/2018	n/a		
PSUSA/10015 /201702	Periodic Safety Update EU Single assessment - ruxolitinib	12/10/2017	01/12/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10015/201702.
II/0034	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier	13/07/2017	n/a		
R/0032	Renewal of the marketing authorisation.	23/02/2017	24/04/2017	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Jakavi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0031	Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information following the completion of two 5-year follow up studies INCB 18424-351 and INC424A2352(long-	15/12/2016	24/04/2017	SmPC and Annex II	In COMFORT-I, after a median follow–up of 61.7 months, the death rate in patients randomised to the ruxolitinib arm was 44.5% (69 of 155 patients) versus 53.2% (82 of 154) in patients randomised to placebo. There was a 31%

	term extensions of pivotal myelofibrosis studies CONFORT-I and COMFORT-II, respectively), thereby addressing one of the outstanding Obligations in Annex II. The RMP (version 7.0) has been updated with completion of post-approval commitments of studies INCB 18424-351 and CINC424A2352. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.69; 95% CI 0.50-0.96; p=0.025). In COMFORT-II, after a median follow-up of 55.9 months, the death rate in patients randomised to the ruxolitinib arm was 40.4% (59 of 146 patients) versus 47.9% (35 of 73 patients) in patients randomized to best available therapy (BAT). There was a 33% reduction in risk of death in the ruxolitinib arm compared to the BAT arm (HR 0.67; 95% CI 0.44-1.02; p=0.062). Long term safety data from two pivotal phase 3 studies assessed 457 patients with myelofibrosis who were treated with ruxolitinib, including patients initially randomised to ruxolitinib (n=301; exposure 0.3–68.1 months, median exposure 33.4 months) and patients who received ruxolitinib after crossing over from control treatments (n=156; exposure: 0.5–59.8 months, median exposure 25.0 months). The cumulative frequency of adverse events in these studies increased proportionally to the increase in the follow-up time. With these updated data, therapy discontinuation due to adverse events was observed in 27.4% of patients treated with ruxolitinib.
PSUSA/10015 /201602	Periodic Safety Update EU Single assessment - ruxolitinib	15/09/2016	18/11/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10015/201602.
IG/0712	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)	03/08/2016	n/a		

II/0025	Update of sections 4.2 and 4.5 of the SmPC in order to include information that the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily should be avoided. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	29/07/2016	SmPC	
IB/0028/G	This was an application for a group of variations. 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) B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	23/02/2016	13/04/2016	SmPC, Labelling and PL	
IB/0027	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/11/2015	13/04/2016	Annex II	
II/0024	Update of section 4.4 of the SmPC in order to add a warning on reported cases of Merkell cell carcinoma in patients treated with ruxolitinib. The RMP version 6.1 has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	22/10/2015	13/04/2016	SmPC	

	data				
PSUSA/10015 /201502	Periodic Safety Update EU Single assessment - ruxolitinib	10/09/2015	n/a		PRAC Recommendation - maintenance
IA/0026	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)	09/06/2015	n/a		
IG/0559	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)	20/05/2015	n/a		
IAIN/0021	A.1 - Administrative change - Change in the name and/or address of the MAH	23/04/2015	13/04/2016	SmPC, Labelling and PL	
PSUSA/10015 /201408	Periodic Safety Update EU Single assessment - ruxolitinib	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0016	Extension of Indication to add treatment of adult patients with polycythaemia vera resistant to or intolerant of hydroxyurea based on the results of Study B2301 (RESPONSE). As a result, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, Annex II has been updated to include a new post-authorisation measure; provision of long-term efficacy and safety data from Study B2301. In addition, the MAH took the opportunity to	22/01/2015	11/03/2015	SmPC and PL	Please refer to the Scientific Discussion Jakavi-H-C-2464-II-16

	implement minor editorial changes in the SmPC. Further, an updated RMP version 5.0 was approved as part of the application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0020	A.7 - Administrative change - Deletion of manufacturing sites	04/02/2015	n/a		
II/0018	Update of section 4.8 of the SmPC, upon request by the CHMP following assessment of LEG 011, with the ADR 'sepsis' and patient-year adjusted rates for sepsis from Study 251, Study 351 and Study 352. C.I.3.z - 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 - Other variation	20/11/2014	11/03/2015	SmPC	In these phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time. Sepsis was added to section 4.8 as a new ADR with frequency category 'common'.
II/0017/G	This was an application for a group of variations. Grouping of two type II variations to update sections 4.5 and 5.2 of the SmPC based on the drug-drug interaction studies CINC424A2102, undertaken to evaluate the effects of ruxolitinib on the pharmacokinetics of a monophasic oral contraceptive, and CINC424A2103, undertaken to evaluate the intestinal CYP3A4 inhibitory effect of ruxolitinib on the pharmacokinetics of orally	20/11/2014	11/03/2015	SmPC	A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

	administered midazolam. The application addresses MEA 003 and MEA 004. A revised RMP version 3.1 has been included as part of the application. 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				
X/0013	To add a new strength 10 mg tablet. Annex I_2.(c) Change or addition of a new strength/potency	24/07/2014	03/10/2014	SmPC, Labelling and PL	
PSUV/0015	Periodic Safety Update	11/09/2014	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	24/07/2014	03/10/2014	SmPC	
IAIN/0014/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a	12/06/2014	n/a		

	manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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) A.7 - Administrative change - Deletion of manufacturing sites				
IB/0012/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	11/03/2014	n/a		

	specification parameter to the specification with its corresponding test method B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised				
PSUV/0011	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
PSUV/0009	Periodic Safety Update	19/09/2013	13/11/2013	SmPC and PL	Update of sections 4.4 and 4.8 of the SmPC in order to warn health care professionals regarding the reported cases of TB and to provide recommendations to evaluate patients for active and inactive TB before starting treatment. The Package leaflet is updated accordingly. Please refer to: Jakavi-H-C-2464-PSUV-0009 EPAR - Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0005	Update of sections 4.2 and 4.4 of the SmPC in order to update the dosing recommendations for patients	19/09/2013	13/11/2013	SmPC, Annex	Further to the CHMP recommendation, the MAH performed simulations to assess the pharmacodynamic time profile of

	with end-stage renal disease (ESRD) undergoing haemodialysis based on the pharmacokinetic (PK) / pharmacodynamic (PD) simulations initiated as a post-authorisation measure agreed during the initial Marketing Authorisation Application (MAA). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity of this variation to correct editorial mistakes and to update the PI in line with version 8.3 of the QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II and PL	ruxolitinib at various doses given once or twice daily in patients with ESRD on haemodialysis. As an outcome of these simulations, a revised starting dose is proposed in patients with ESRD and sections 4.2 and 4.4 of the SmPC were updated to reflect the new dosing recommendation.
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)	08/10/2013	03/10/2014	SmPC	
IA/0007/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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/08/2013	n/a		
II/0006	Update of section 4.4 of the SmPC in order to include a warning on the potential risk of Progressive multifocal leukoencephalopathy (PML). The Package Leaflet was updated accordingly.	27/06/2013	13/11/2013	SmPC and PL	A case of PML has been reported with Jakavi as a follow-up report in study CINC424AGB02. Further to the MAH review of the company safety databases and literature, another potential case of PML has been identified. As a

	In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				consequence, section 4.4 of the SmPC has been updated to include a warning on the potential risk of PML. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. The PL has been updated accordingly.
IB/0003/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/02/2013	n/a		
IB/0002/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished	20/02/2013	13/11/2013	SmPC, Labelling and	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished			PL	

	product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of manufacturing sites A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IB/0004	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	19/02/2013	n/a		
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		