Olumiant®

(baricitinib)

2 mg and 4 mg, film-coated tablets

Summary of Risk Management Plan (RMP)

Summary of the risk management plan (RMP) for Olumiant (baricitinib)
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.
The RMP summary of Olumiant is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le medicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Olumiant in Switzerland is the „Arzneimittelinformation/ Information sur le médicament“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.
Eli Lilly is fully responsible for the accuracy and correctness of the content of this published summary RMP of Olumiant.

I. The Medicine and What It Is Used For

Olumiant is authorised for moderate-to-severe RA, moderate-to-severe AD, and severe AA (see SmPC for the full indication). It contains baricitinib as the active substance and it is given by mouth.

Further information about the evaluation of Olumiant's benefits can be found in Olumiant's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Olumiant, together with measures to minimise such risks and the proposed studies for learning more about Olumiant's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Olumiant, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Olumiant is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Olumiant are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Olumiant. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Herpes zoster • VTE
Important potential risks	• Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • Gastrointestinal perforation • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero
Missing information	• Long-term safety • Use in very elderly (≥75 years) • Use in patients with evidence of hepatitis B or hepatitis C infection • Use in patients with a history of or current lymphoproliferative disease • Use in patients with active or recent primary or recurrent malignant disease • Use in paediatric patients

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; JAK = Janus kinase; MACE = major adverse cardiovascular event; PML = = progressive multifocal leukoencephalopathy; VTE = venous thromboembolic event.

II.B. Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk: Herpes Zoster	
Evidence for linking the risk to the medicine	In the clinical trial (CT) development programmes, observed cases of herpes zoster (HZ) have been predominantly classified as nonserious (89% in rheumatoid arthritis [RA], 100% in atopic dermatitis [AD], and 95% in alopecia areata [AA]). The majority (95% RA, 100% AD, and 95% in AA) of the reported cases were classified by the investigator as mild to moderate in severity. A similar profile has also been reported from everyday clinical practice since baricitinib was first marketed in the European Union (EU) for RA on 13 February 2017. As would be expected in a medical condition that is usually treated by specialists, the majority of HZ cases have been readily diagnosed, managed, and typically resolved without long-term sequelae. More clinically important manifestations of HZ have been reported very rarely with cases in which the rash spreads beyond the primary or adjacent dermatomes (multidermatomal HZ being reported in 8.5% of patients that reported HZ in RA CTs, 0.1% patients in AD CTs, and no patients in AA CTs); HZ was associated with motor nerve involvement in 0.1% of cases in RA and none in AD and AA. A common complication of this infection, irrespective of the cause, is post-herpetic neuralgia. This has been reported in a low proportion of patients who developed herpes zoster (5% in RA, 0% in AD and AA). In the AD CT development programme, 1.6% of the patients had a HZ infection. There were no serious cases of HZ reported and all events that were reported were mild or moderate in severity. No patients discontinued treatment due to HZ. The majority (88.9%) of events were readily diagnosed, managed, and resolved without sequelae. In the AA CT development programme, 1.6% of the patients developed a HZ infection. There was 1 serious case of HZ that also was severe. All other cases were nonserious and mild or moderate in severity. No patients discontinued treatment due to HZ. All cases resolved without sequelae.
Risk factors and risk groups	A notable proportion of the cases of HZ (26.4%) reported in the baricitinib RA CTs were reported from Japan, where the reporting rate was higher than that from any other countries. Whether this represents a true risk factor or representative of other factors such as detection bias are unclear. Similar findings were seen with tofacitinib. Heavily pretreated RA elderly patients appear to be at higher risk of HZ.

Risk minimisation measures	[Routine risk minimisation measures:] Summary of Product Characteristics (SmPC) Section 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients be brought up to date with all immunisations. Patient information leaflet (abbreviated as PIL or PL throughout) Sections 2 and 4 • PL Section 2 advises that the patient should tell their doctor if they develop signs of shingles. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card
Additional pharmacovigilance (PV) activities	Observational post-marketing safety studies to monitor the incidence of HZ in patients exposed to baricitinib. RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Venous thromboembolic events	
Evidence for linking risk to the medicine	Venous thromboembolism is considered an ADR of baricitinib treatment. A numerical imbalance in reports of DVT and PE during the 16-week placebo-controlled portion of the baricitinib CTs was noted in clinical development (5 cases vs. 0). This imbalance formed the basis for VTE being classified as an important potential risk. Further data, including the imbalances noted in the AD clinical programme led to VTE being classified by the company as an ADR, supporting the change to an important identified risk. In the observational study I4V-MC-B023, meta-analysis of results from 14 data sources shows a significantly elevated incidence rate ratio for VTE in baricitinib compared to TNFi-treated RA cohorts. The incidence rate of VTE was greater among patients with treated with baricitinib than with TNFi. Data analysed for this study was primarily from insurance claims records and also included data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for VTE, including age, sex, cancer history, cardiovascular disease, immune disorders, diabetes, prescription medication use including treatments for RA, and health care resource utilisation.

Risk factors and risk groups	All patients who developed VTE had recognised and well-established risk factors for thromboembolism, namely older age, obesity, NSAID use, and medical history of DVT and PE.

Risk minimisation measures	[Routine risk minimisation measures:]
	SmPC Sections 4.4 and 4.8
	(DVT and PE)
	PIL Section 2
	
	• SmPC Section 4.4 advises that
	  o Olumiant should be used with caution in patients with risk factors for VTE and that if clinical features of VTE occur, treatment should be discontinued and patients should be evaluated promptly and appropriately treated.
	• PIL Section 2 advises patients:
	  o To talk to their doctor or pharmacist before and during treatment if they have previously had a VTE or if they develop symptoms of VTE
	  o Olumiant should be used with caution in patients with risk factors for VTE
	  o That treatment should be discontinued if clinical symptoms of VTE occur.
	
	[Additional risk minimisation measures:]
	• Healthcare Professional Educational Material
	• Patient Alert Card
	• Direct Healthcare Professional Communication

Additional PV activities	Observational post-marketing safety studies to compare the incidence of VTE, including VTE validated based on clinical information, among patients exposed to baricitinib being treated for moderate-to-severe: RA: • EU registries • Nordic healthcare study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers)	
Evidence for linking the risk to the medicine	The association between immunomodulatory products like baricitinib and malignancy is largely theoretical and based on a putative effect on the immune system and the capacity for cancer immunosurveillance (a process by which the body's immune system recognises transformed cells to inhibit the growth of neoplastic tissue). In contrast, it is also suspected

	that the chronic inflammation present in RA and other autoimmune conditions, rather than its treatment, may underlie the increased incidence of lymphoma observed in these patients compared to the general population, through its continuous stimulation of B cells (Baecklund et al. 2006; Beyaert et al. 2013) or through induction of Epstein Barr virus replication (Hollander et al. 2015). Similarly in patients with AD, there is a slightly increased risk of lymphoma, with severity of AD as a significant risk factor (Legendre et al. 2015; Paller et al. 2018). The literature regarding risk of various other malignancies in patients with AD is inconclusive with some literature suggesting increased risks for skin cancers and others suggesting no increased risk (Andersen et al. 2017; Paller et al. 2018). A systematic literature review (Lee et al. 2019b) found no increased risks for haematologic, cutaneous, or solid organ malignancies among patients with AA. The single exception was that thyroid cancer was found to be more prevalent among patients with AA (OR=1.89, 95% CI: 1.53-2.34) (Lee et al. 2019b). The most commonly reported malignancies in the baricitinib RA clinical development programme have been breast, lung, colorectal, prostate, and renal, which are malignancies more frequently observed in the general RA population (Raheel et al. 2016). Uncertainties therefore remain as to whether the malignancies observed are reflective of disease morbidity in the target population or a true effect of treatment. In the AD and AA programme, very few malignancies were reported; 5 cases in AD, with 1 lymphoma and 4 non-melanoma skin cancer, and 3 cases in AA, with 1 lymphoma, 1 breast cancer, and 1 non-melanoma skin cancer. The number and type of malignancies reported were in line with the age range of this patient population.
Risk factors and risk groups	No specific risk groups or specific risk factors have been identified from the clinical development programme for baricitinib.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.4 PIL Section 2 • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] • Direct Healthcare Professional Communication • Healthcare Professional Educational Material • Patient Alert Card
Additional PV activities	Observational post-marketing safety studies to compare the incidence of malignancy in patients exposed to baricitinib with patients exposed to other medications used for:

	Moderate-to-severe RA: • EU registries • Nordic healthcare study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) Moderate-to-severe AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML)	
Evidence for linking the risk to the medicine	As would be expected from its mode of action, various infections were consistently observed throughout the clinical development programme for baricitinib and, overall, affected approximately one-half of the RA and AD study populations and one-third of the AA study population exposed to baricitinib, respectively. The evidence was considered sufficient to conclude that some infections (such as upper respiratory tract infections, HZ, herpes simplex, pneumonia and urinary tract infection) were adverse effects of the product. The profiles of infections observed were mainly of a nonserious nature with rates consistent with those observed with other RA therapies. In AD randomised CTs, serious infections were rare and numerically less frequent with baricitinib treatment than with placebo. This was also the case for serious herpes simplex infections. In the All BARI AA analysis set, few patients reported serious infections with an incidence rate (IR) of 0.6 events per 100 patient-years, and there have been no reports of serious herpes simplex or tuberculosis infections. In RA, more clinically significant infections, including opportunistic infections, have been reported rarely and were generally well managed. Pneumonia has been added to the SmPC as an adverse effect of baricitinib at the request of the PRAC. The evidence source for the request to add PML to this safety concern was on the basis of a single case report with another JAK inhibitor. To date, no cases of PML have been reported with baricitinib. In the AD and AA populations, there have been no reports of opportunistic infections with baricitinib. Results from the meta-analysis of the B023 observational study show a numerically greater incidence rate ratio of incident serious infection with baricitinib compared to TNFi in patients with RA. The incidence rate of first serious infection was greater among patients treated with baricitinib than with TNFi, and the difference was 0.57 (95% CI -0.07, 1.21) per 100 PY. Serious infection was defined as infection requiring

	hospitalisation. Opportunistic infections were not analysed separately due to the difficulty of identification in the selected data sources. Data analysed for this study came primarily from health insurance claims records and included some data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for serious infection, such as age, sex, immune disorders, diabetes, immune disorders, ischaemic heart disease, prescription medication use including glucocorticoids, and count of previous bDMARDs, and health care resource utilisation.
Risk factors and risk groups	Analysis of the CT data for baricitinib in RA shows that concomitant corticosteroids use, prior biological medicines use, being underweight, overweight, or obese, living in the Asian region, and advanced age (≥50 years old) are the key risk factors for serious infections. No specific risk factors for serious infections have been identified for AD patients. A serious form of herpes simplex (eczema herpeticum - EH) has been reported and is associated with poor skin condition that may occur in AD.

Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 PL Section 2 • SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. It also recommends that if an infection develops, the patient should be monitored carefully and Olumiant should be temporarily interrupted for any infection that is not responding to standard therapy. Treatment should not be resumed until the infection resolves. • SmPC Section 4.4 advises that patients should be screened to rule out active tuberculosis (TB) and active viral hepatitis before starting Olumiant. • SmPC Section 4.4 advises that live, attenuated vaccines should not be used during or immediately prior to treatment. It also recommends that, prior to starting treatment, all patients be brought up to date with all immunisations. • Section 2 of the PL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patients that they should tell their doctor if they get signs of TB, HZ or have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card • DHPC
Additional PV activities	Observational post-marketing safety studies to compare the incidence of serious and opportunistic infections (including TB, *Candida*, and PML) in patients exposed to baricitinib with patients exposed to other medications used for moderate-to-severe: RA: • EU registries • Nordic healthcare study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Myelosuppression (agranulocytosis)	

Evidence for linking the risk to the medicine	Treatment with baricitinib in RA was associated with decreased neutrophil counts in 11.5% of patients for RA, 11.4% in AD, and 17.3% in AA, and this was consistent across CTs. The frequency with which the absolute neutrophil count (ANC) fell transiently to <500/mm^3 (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4 neutropenia) was very low in RA (0.14%) and AA (0.3%) and none in AD. Importantly, the observed neutropenia, regardless of CTCAE grade, was not associated with a higher risk of serious infections. Although "neutropenia <1000 cells/mm^3" is an acknowledged adverse effect of baricitinib treatment and listed as such in the SmPC, there is no current evidence to support agranulocytosis (defined as <100 cells/mm^3) as an important potential risk independent of the "Serious Infections" already included as a safety concern in the EU risk management plan (RMP), this takes into account that the well-known outcome of low white cell counts is infection.
Risk factors and risk groups	No risk factors for neutropenia or myelosuppression (agranulocytosis) have been identified. Agranulocytosis during baricitinib treatment either in clinical development or post-marketing has not been observed.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2,4.4, 4.8, and 5.3 PL Sections 2 and 4 • SmPC Sections 4.2 and 4.4 recommend that treatment should not be initiated or should be temporarily interrupted in patients with white cell counts or a haemoglobin that is below a certain level. • PL Section 2 advises patients that they may need blood tests prior to or during treatment to check if they have a low red or white blood cell counts. [Additional risk minimisation measures:] None
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of myelosuppression in patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Myopathy including rhabdomyolysis	

Evidence for linking the risk to the medicine	Although increased creatinine phosphokinase (CPK) >5x upper limit of normal (ULN) is a common adverse effect of baricitinib listed in the SmPC, the strength of evidence linking the muscle enzyme (CPK) elevations observed during treatment with clinically significant or concerning adverse outcomes such as myopathy or severe muscle damage (rhabdomyolysis) is weak. As described in the SmPC, treatment with baricitinib was associated with a rapid (within 1 week) increase in CPK values. In RA, the mean CPK value plateaued after approximately 8 to 12 weeks of treatment, while in AD and AA it varied throughout therapy. Discontinuation of baricitinib due to an increased CPK or musculoskeletal adverse event (AE) symptoms was uncommon in RA (0.4%) and AD (0.1%) and no discontinuations were reported in AA. In addition, there have been no confirmed cases of rhabdomyolysis from CT and from limited information from post-marketing experience to date.
Risk factors and risk groups	As the incidence rate of muscle symptoms in CT development has been so low and no confirmed cases of rhabdomyolysis have been reported, it is not possible to identify any specific patient risk factors for these conditions.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.8 (increases in CPK) PL Section 4 (increases in CPK) [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of myopathy including rhabdomyolysis in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Potential for drug-induced liver injury	
Evidence for linking the risk to the medicine	Within the RA CT programme, increases in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to ≥5 and ≥10× ULN were reported in 1.2% and 0.3% patients, respectively, and these increases are considered to be adverse effects of baricitinib. Within the AD CT programme increases in the liver enzymes ALT and AST to ≥5 and ≥5× ULN were reported in 0.3% and 0.4% patients, respectively, with no patients having an increase of ≥10× ULN. In the AA CT programme, 0.8% and 0.5% of patients had increases of

	ALT and AST ≥5 ×ULN, respectively, and 0.1% and 0.2% had increases of ALT and AST ≥10 × ULN, respectively. None of these enzyme changes were linked to clinically significant evidence of drug-induced liver injury (DILI). Only 0.2% of AEs for hepatic disorders were considered by the investigators to be serious in RA, 0.1% (1 case) in AA, and none in AD. Post-marketing, there have been few reports in patients with RA describing the increased liver enzymes typically seen in the CT programme, but none have involved evidence of actual liver injury.
Risk factors and risk groups	No risk groups or specific risk factors have been identified from the clinical development programmes, although concurrent use of baricitinib with potentially hepatotoxic medicinal products, such as methotrexate (MTX), results in a higher frequency of liver enzyme elevations. In the AD and AA programmes, no specific risk factors have been identified.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 • SmPC Section 4.2 recommends that Olumiant should not be used in patients with severe hepatic impairment. • Section 4.4 recommends that if increases in ALT or AST are observed and DILI is suspected, Olumiant should be interrupted. • •Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function. [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of potential DILI among patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Gastrointestinal perforation	
Evidence for linking the risk to the medicine	Although there is a pharmacologically plausible basis for an association between baricitinib and gastrointestinal (GI) perforation, there are insufficient data to establish it as an adverse effect of treatment at this time. The frequency of cases indicative of GI perforation is very low in CTs (less than 0.1%

	of patients with RA, no cases observed in patients with AD and AA), and in each case, there have been significant confounding factors, such as use of steroids and GI surgery. The overall incidence rate of GI perforations was 0.04 events per 100 patient-years (PY) in RA, and this is within the published rates reported in patients with RA (0.02-0.39 per 100 PY). Patients with RA may be at an increased risk of GI perforation because of prescribed medication, and/or because of the consequences of the disease process itself (e.g., vasculitis). As a result, the determination of whether or not the limited observations reflect underlying disease morbidity as opposed to an adverse effect of baricitinib is challenging and will be systematically monitored in the proposed studies in the PV plan for the product. Similar risks are not seen with AD and AA, and systemic steroid use is limited to times of severe AD flares and to more extensive manifestation of AA, respectively.
Risk factors and risk groups	No specific risk factors for GI perforation have been identified with baricitinib.
Risk minimisation measures	[Routine risk minimisation measures:] None [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of GI perforations in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Major adverse cardiovascular events as an outcome of hyperlipidaemia	
Evidence for linking the risk to the medicine	Consistent with a pharmacologic effect of Janus kinase (JAK) inhibition, dose-dependent increases in blood lipid levels (including total cholesterol, triglycerides, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) were observed throughout the RA clinical development programme for baricitinib. The increase in LDL-C and all other parameters occurred within the first 12 weeks of treatment and remained stable thereafter. In the AD and AA populations, increases in lipids were seen by 12 weeks for total cholesterol, LDL and HDL. Mean values for HDL remained fairly stable after Week 12. Mean total and

	LDL cholesterol increased through Week 52. Triglyceride changes were small and not different from placebo. The overall evidence was considered sufficient to conclude that hypercholesterolaemia was an adverse effect of the product. Long-term exposure to increases in blood lipids in the general population would be expected to be associated with adverse cardiovascular (CV) outcomes (major adverse cardiovascular event [MACE]), but literature sources indicate that they may not be harmful to patients with RA as the benefits of suppression of inflammation may outweigh the risk of the lipid changes. In this regard, few MACE were observed in RA clinical development and no relationship was observed between MACE and LDL-C increases. As noted in the original RA submission, the increases in LDL-C observed with baricitinib treatment are responsive to statin treatment, and no direct link to major adverse CV outcomes has been established to date. No cases of MACE were seen in the AD clinical programme and 1 case was reported in AA clinical development in a patient with multiple risk factors (tobacco use, obesity, hypercholesterolemia, atrial fibrillation, and hypertension). . In a randomised post-authorisation safety study in patients with RA aged 50 years or older with at least 1 additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared with TNF inhibitors. Results from the meta-analysis of the B023 observational study show a numerically greater incidence rate ratio for MACE in baricitinib compared with TNFi- treated RA cohorts. The incidence rate of MACE was greater among patients treated with baricitinib than with TNFi. Data analysed for this study were primarily from insurance claims records and included some data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for MACE, such as age, sex, history of cardiovascular disease, prescription medication use, and health care resource utilisation. Rheumatoid arthritis, AD, and AA are, however, chronic conditions and, in the case of RA, one in which patients are already at higher risk of CV disease. As such, patients treated with baricitinib in usual clinical practice may be treated for several years and in higher numbers than exposed in CTs. As the long-term effects of these lipid changes on adverse CV outcomes in these circumstances are uncertain, MACE has been classified as an important potential risk warranting further systematic study in the PV Plan of this RMP.
Risk factors and risk groups	No specific risk factors for hyperlipidaemia have been identified with baricitinib. Similarly, the number of patients in

	whom MACE has been reported in CTs remains very low in RA and AA and none were reported in AD. As a result, no specific risk factors for MACE have been identified with baricitinib. Based on RA CT data, compared to the patients without MACE, patients with MACE were more likely to have the following CV risk factors at baseline: older age, longer disease duration, cigarette smoking, prior cardiac disorder, hypertension, obesity, and hypercholesterolaemia. However, the risk factors for MACE observed in this CT population are typical of risk factors for MACE in the general population. The extent to which prevalence of cardiovascular disease (CVD) in patients with RA is a contributory factor is unknown.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Section 2 and 4 • SmPC Section 4.4 advises that lipid parameters should be assessed at 12 weeks following treatment initiation and thereafter according to international guidelines for hyperlipidaemia. Olumiant should be used with caution in patients with risk factors for MACE. • PL Section 2 advises patients that they may need blood tests while taking Olumiant to check if they have a high cholesterol level and to speak to their doctor if they have or have previously had heart problems. [Additional risk minimisation measures:] • Healthcare Professional Educational Material (lipid monitoring) • Patient Alert Card • Direct Healthcare Professional Communication
Additional PV activities	Observational post-marketing safety studies to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study • Randomised, controlled post-authorisation safety studies in US (JAJA/JAJD) AD • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Foetal malformation following exposure in utero	
Evidence for linking the risk to the medicine	Studies in rats and rabbits dosed in excess of the maximum human exposure have shown reproductive toxicity when baricitinib was dosed during the early stages of pregnancy.

	These animal studies indicate that baricitinib may have an adverse effect on bone development in utero at these higher dosages. There is no current evidence of similar findings in the babies of mothers who have been treated with baricitinib during pregnancy but experience at this time is very limited. As a result, the effects of baricitinib on the bone development of the baby prior to birth are unknown and, as advised in the prescribing information, women of childbearing potential should not become pregnant when treated with baricitinib.
Risk factors and risk groups	No risk factors have been identified as there are currently no data from CTs or post-marketing data sources in human pregnancy indicative of the bone effects observed in the nonclinical studies. The highest risk period is considered to be the first 12 weeks of pregnancy; however, pregnant or lactating women were excluded from CTs with baricitinib, and experience in human pregnancy is limited. Therefore, neither specific duration of treatment nor risk period have been identified.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.3, 4.6, and 5.3 PIL Section 2 • SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication. • SmPC Section 4.6 advises that patients of childbearing potential should use effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last treatment. • Section 4.6 of the SmPC also advises that a decision must be made whether to discontinue breastfeeding or to discontinue Olumiant therapy. • PL Section 2 o States that patients should not take Olumiant if they are pregnant or think that they may be pregnant o Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking the medicine o States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment o States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card

Additional PV activities	Observational post-marketing safety studies to monitor the incidence of foetal malformation following exposure in utero among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Long-term safety	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 No additional recommendations are included in the SmPC or PL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor long-term safety in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Use in very elderly (≥75 years)	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 (lymphocytosis) and 5.2 PIL Section 3 • SmPC Section 4.2 recommends that in patients, ≥75 years, a starting dose of 2 mg is appropriate. [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • Nordic healthcare study AD: • Nordic healthcare study

	See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Use in patients with evidence of hepatitis B or hepatitis C infection	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 • SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if the test is positive, a liver specialist should be consulted • Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] None.
Important missing information: Use in patients with a history of or current lymphoproliferative disease	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.4 PL Section 2 • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None
Important missing information: Use in patients with active or recent primary or recurrent malignant disease	
Risk minimisation measures	[Routine risk minimisation measures:] PIL Section 2 • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer [Additional risk minimisation measures:] None
Important missing information: Use in paediatric patients	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.2 PIL Section 2 • PL Section 2 advises that Olumiant is not for use in children and adolescents younger than 18 years old. [Additional risk minimisation measures:]

	None
Additional PV activities	RA and AD: • Off-label use in children (Clinical Practice Research Database [CPRD]) See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: AD = atopic dermatitis; ADR = adverse drug reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; BARI = baricitinib; CPK = creatinine phosphokinase; CT = clinical trial; CTCAE = Common Terminology Criteria for Adverse Events; CV = cardiovascular; CVD = cardiovascular disease; DILI = drug-induced liver injury; DVT = deep vein thrombosis; EU = European Union; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; JAK = Janus kinase; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; NSAID = non-steroidal anti-inflammatory drug; PE = pulmonary embolism; PL = patient information leaflet; PML = progressive multifocal leukoencephalopathy; PV = pharmacovigilance; PY = patient years; RA = rheumatoid arthritis; RMP = risk management plan; SmPC = Summary of Product Characteristics; TB = tuberculosis; ULN = upper limit of normal; VTE = venous thromboembolic events

II.C. Post-authorisation Development Plan

II.C.1. Studies that Are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Olumiant.

II.C.2. Other Studies in Post-authorisation Development Plan

Study short name: **Study I4V-MC-B011**; Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries

Purpose of the study: The rationale for conducting this study is to characterise the long-term safety of baricitinib among RA and AD patients treated in routine clinical care in Nordic countries using a retrospective study design.
Specifically, the objectives include 1) to compare the incidence rates and profiles of: serious and opportunistic infections, MACE, malignancies, and VTE in RA and AD patients (separately) with long-term exposure to baricitinib, which will be compared to similar patients with long-term exposure to other indicated medications; and 2) to describe the occurrence of lymphoma; HZ; opportunistic and fungal infections; GI perforations; and serious disorders of the muscle, bone marrow, blood lipids, white blood cell count, and liver.

A secondary objective is to monitor the incidence of the major outcomes among patients aged 75 years or older. Another secondary objective is to assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active TB, or active viral hepatitis and the monitoring of lipid levels in relation to baricitinib use in routine clinical care.

Study short name: **Study I4V-MC-B012**; Observational post-marketing surveillance in 3 EU registries

Purpose of the study: The rationale for this study is to provide prospective, long-term safety monitoring for baricitinib in routine clinical practice in the EU.

The study objectives are to monitor the incidence rate and profile of various serious and opportunistic infections, MACE, malignancies, and VTE in EU patients with RA with long-term exposure to baricitinib. This information will be compared to patients with long-term exposure to other medications used for moderate-to-severe RA. A second objective will aim to describe the occurrence of lymphoma; HZ; opportunistic infections; GI perforations; and serious disorders of the muscle, bone marrow, white blood cell count, and liver.

Study short name: **Study I4V-MC-B016**; Observational descriptive cohort study

Purpose of the study: Use of baricitinib in children and adolescents is classified as missing information. This study will describe the proportion of baricitinib prescribing in the United Kingdom that is off-label to children and adolescent patients to help quantify the level of this safety concern.

Study short name: **Study I4V-MC-B025;** Observational, multinational, cross-sectional survey

Purpose of the study: To assess the effectiveness of the updated baricitinib additional risk minimisation activities in Europe in prescribers treating patients with RA, AD, or AA.

This survey will also assess the effectiveness of a DHPC distributed to dermatologists and rheumatologists to communicate changes in the SmPC

Study short name: **Study I4V-MC-JAJA/ I4V-MC-JAJD** Evaluation of the safety of baricitinib in patients with RA

Purpose of the studies: These studies will be combined to help determine the safety of baricitinib, a type of medicine called a Janus kinase (JAK) inhibitor, in patients with rheumatoid arthritis. These studies will compare the safety of 2 doses (2 mg and 4 mg) of baricitinib to the standard of care drugs called tumour necrosis factor inhibitors (TNFi). To compare the safety of the study drugs, a review of health events that happen during the studies will be completed. The main health event to be reviewed is clots that occur in a vein (called venous thromboembolism). Other health events being reviewed are blood clots in arteries, major cardiac (heart) events, cancers, and infections.

Study short name: Drug Utilisation Study to Assess Prescribing Patterns of Baricitinib

Purpose of study: This drug utilisation study aims to measure the effectiveness of newly implemented prescribing recommendations. This will be accomplished by evaluating prescribing behaviours after implementation of the recommended changes.

Major Changes to the Risk Management Plan over Time

June 2017: VTE added as an important potential risk.

June 2017: In vitro study to investigate the inhibitory effect of baricitinib on OAT2 completed.

September 2017: Vaccine study completed.

March 2020: EU PAS Study I4V-MC-B010 completed.

February 2021 Indication atopic dermatitis

July 2022 VTE, MACE and malignancy compared to TNF-inhibitors

May 2023 Indication alopecia areata

This summary was last updated in 06-2023