Summary of risk management plan for Cibinqo (abrocitinib)

This is a summary of the risk management plan (RMP) for Cibinqo. The RMP details important risks of Cibinqo, how these risks can be minimised, and how more information will be obtained about Cibinqo risks and uncertainties (missing information).

Cibinqo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cibinqo should be used.

This summary of the RMP for Cibinqo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cibinqo's RMP.

I. The Medicine and What It Is Used For

CIBINQO is indicated for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy (see SmPC for the full indication). It contains abrocitinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Cibinqo's benefits can be found in Cibinqo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/cibinqo

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

Important risks of Cibinqo, together with measures to minimise such risks and the proposed studies for learning more about Cibinqo '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 Cibinqo, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events will be collected continuously and regularly analysed, including PSUR 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 Cibinqo is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Cibinqo 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 Cibinqo. 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);

Table 1. List of Important Risks and Missing Information

Important identified risks	Thrombotic events including pulmonary embolism
	Herpes zoster
Important potential risks	Serious and opportunistic infections
	Malignancy
	MACE
	Myopathies (including rhabdomyolysis)
	Gastrointestinal perforation
	Embryofoetal toxicity following exposure in utero
	Impaired bone growth and development if used off-label in paediatric patients <18 years-of-age
	Fractures
Missing information	Long-term safety

II.B Summary of Important Risks

Table 2. Important Identified Risk - Thrombotic Events including Pulmonary Embolism

Evidence for linking the risk to the medicine	Approved therapies of the Janus kinase (JAK) inhibitor class are associated with or being investigated for the risk of VTE including pulmonary embolism. Adjudicated VTEs (deep venous thrombosis and pulmonary embolism) were assessed in the abrocitinib development program.
Risk factors and risk groups	There were an insufficient number of cases to analyse risk factors in the clinical trial data. Risk factors for DVT/PE in the general population also apply to patients with AD including older age, obesity, a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization.

Table 2. Important Identified Risk - Thrombotic Events including Pulmonary Embolism

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 3. Important Identified Risk - Herpes zoster

Evidence for linking the risk to the medicine	Clinical study data with abrocitinib and understanding of JAK mechanisms based on data from the JAK class of therapies.
Risk factors and risk groups	For all herpes zoster events (regardless of adjudication as an opportunistic infection), age ≥65 years, confirmed ALC <1.0 (10^3/mm^3) prior to event, a medical history of herpes zoster, region and dose of 200 mg were identified as the most significant risk factors in a multivariate analysis. There was no clear pattern of risk across the regions. In addition, while not identified in the multivariate model, the IR for herpes zoster, early in treatment, was higher in subjects with severe baseline AD compared to subjects with moderate baseline AD. There was an insufficient number of events of opportunistic herpes zoster to identify risk factors from the clinical data.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card

Table 3. Important Identified Risk - Herpes zoster

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 4. Important Potential Risk – Serious and Opportunistic Infections

Evidence for linking the risk to the medicine	Approved therapies of the JAK inhibitor class are associated with or are being investigated for risk of serious infections and opportunistic infections. Serious and adjudicated opportunistic infections were assessed in the abrocitinib development program.
Risk factors and risk groups	No risk factors were identified for serious infections.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Prescriber Brochure Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 5. Important Potential Risk - Malignancy

Evidence for linking the risk to the medicine	Clinical trial data and understanding of JAK mechanisms based on the data from the JAK class.

Table 5. Important Potential Risk - Malignancy

Risk factors and risk groups	There was an insufficient number of events for risk factor or subgroup analysis. However, it can be noted that in review of cases, all subjects with squamous cell carcinoma were ≥63 years of age. The 2 subjects experiencing prostate cancer were 68 and 73 years old. The subject with adenocarcinoma gastric was 78 years old.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use PL Section 2 Additional risk minimisation measures: Prescriber Brochure
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 6. Important Potential Risk – MACE

Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for potential risk of MACE.
Risk factors and risk groups	There were too few deaths for risk factor analysis. Traditional risk factors for MACE, in addition to hyperlipaemia, such as age and smoking are likely important in the AD population.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use (lipid monitoring, including in the setting of a high burden of cardiovascular risk) SmPC Section 4.8 Undesirable effects (hyperlipidaemia only) PL Section 2 and 4 Additional risk minimisation measures: Prescriber Brochure (lipid monitoring) Patient Care (lipid monitoring)

Table 6. Important Potential Risk – MACE

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 7. Important Potential Risk – Myopathies (including Rhabdomyolysis)

Evidence for linking the risk to the medicine	Clinical trial data and based on the data from the JAK class. Approved JAK inhibitors are being investigated for potential risk of myopathy (including rhabdomyolysis).
Risk factors and risk groups	There were insufficient events to establish risk factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects (Blood creatine phosphokinase increase)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 8. Important Potential Risk – Gastrointestinal Perforation

Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for potential risk of GI perforation.
Risk factors and risk groups	There was an insufficient number of events to establish risk factors. The subject with the serious event of duodenal ulcer haemorrhage and non-serious event of gastritis erosive was 83 years old.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration

Table 8. Important Potential Risk – Gastrointestinal Perforation

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 9. Important Potential Risk – Embryofoetal Toxicity Following Exposure in Utero

Evidence for linking the risk to the medicine	Abrocitinib did not cause malformations in pregnant rats or rabbits. Approved therapies in the JAK inhibitor class are being investigated for potential risk of foetal malformation following exposure in utero.
Risk factors and risk groups	Risk of foetal malformation pertains only to women of childbearing potential who become pregnant while receiving abrocitinib or and for at least 4 weeks after treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, Pregnancy and Lactation Additional risk minimisation measures: Prescriber Brochure Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 10. Important Potential Risk – Impaired Bone Growth and Development if Used Off-label in Paediatric Patients <18 Years-of-Age

Evidence for linking the risk to the medicine	In studies to support the use of abrocitinib in children <12 years old, administration of abrocitinib to juvenile rats (comparable to a 3-month-old human) resulted in macroscopic and microscopic bone findings. In toxicity studies of up to 1 month of abrocitinib dosing in rats at an age comparable to adolescent human age a microscopic bone dystrophy finding, considered transient and reversible, was noted, and exposure margins at which no bone finding was noted were 6x to 6.4x the unbound human AUC at a clinical dose of 200 mg QD. No bone findings were observed in rats at any dose in the 6-month toxicity study in any of the toxicity studies in cynomolgus monkey.

Table 10. Important Potential Risk – Impaired Bone Growth and Development if Used Off-label in Paediatric Patients <18 Years-of-Age

Risk factors and risk groups	There is a potential risk for patients <18 years of age.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration PL Section 2
Additional pharmacovigilance activities	Additional pharmacovigilance activities: B7451085: A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in EU using Electronic Healthcare Data B7451015: Long-term Extension Study B7451015: Adolescent Imaging Substudy See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 11. Important Potential Risk – Fractures

Evidence for linking the risk to the medicine	In toxicity studies of up to 1 month of abrocitinib dosing in rats at an age comparable to adolescent human age of ≥12 years, a microscopic bone dystrophy (metaphysis; growth plate was normal) finding, considered transient and reversible, was noted, and exposure margins at which no bone finding was noted were 6x to 6.4x the unbound human AUC at a clinical dose of 200 mg QD. In toxicity studies of up to 1 month of abrocitinib dosing in rats at an age comparable to adolescent human age a microscopic bone dystrophy finding, considered transient and reversible, was noted, and exposure margins at which no bone finding was noted were 6x to 6.4x the unbound human AUC at a clinical dose of 200 mg QD. No bone findings were observed in rats at any dose in the 6-month toxicity study in any of the toxicity studies in cynomolgus monkey.
Risk factors and risk groups	There was an insufficient number of events to establish risk factors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 Preclinical safety data
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension study

Table 12. Missing Information – Long-term Safety

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU B7451015: Long-term Extension Study See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of Abrocitinib-Pfizer Europe MA EEIG.

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

B7451084: An Active Surveillance Study to Monitor the Real-World Safety of Abrocitinib among Patients with Atopic Dermatitis in the EU

Purpose of the study:

Based on data from Cibinqo clinical program, it is of MAH's opinion that it is important to monitor the real-world safety of Cibinqo following its authorization in the EU. An active safety surveillance study will assess safety endpoints of interest with Cibinqo in the post-approval setting.

The study objective is to estimate incidence rates of safety endpoints of interest among AD patients who initiate treatment with Cibinqo and AD patients receiving appropriate systemic treatments for AD in the real-world setting.

The following are the primary safety endpoints of interest:

- Thrombotic events including pulmonary embolism,
- Herpes zoster,
- Serious infection (including subtypes of herpes simplex and eczema herpeticum and pneumonia)
- Opportunistic infection,
- Rhabdomyolysis,

- Gastrointestinal perforation,
- Malignancy,
- MACE, and
- Fractures

B7451085: A Drug Utilization Study to Evaluate the Effectiveness of Risk Minimisation Measures for Abrocitinib in the EU Using Electronic Healthcare Data

Purpose of the study:

To mitigate the risks associated with abrocitinib, required routine RMMs including the SmPC and package leaflet are being employed. In order to minimise important risks with the use of Cibinqo, the MAH has also implemented additional RMMs: an educational program intended to enhance the communication of the risk and risk minimisation practices to HCPs and patients. The program includes a Prescriber Brochure and a Patient Card.

The MAH plans to evaluate the effectiveness of RMMs being implemented for abrocitinib. The proposed study will be designated as a PASS.

The research question will be: Do HCPs in the EU adhere to the recommendations for the use of abrocitinib described in the SmPC and prescriber brochure?

The study objectives are to evaluate, to the extent measurable in the available routinely collected date, indicators of HCPs' adherence to the prescribing information in accordance with the abrocitinib SmPC and prescriber brochure, specifically:

- Indicators of adherence to performing laboratory tests of complete blood count (CBC), lipid panel, hepatitis B/C and tuberculosis (TB) screening prior to initiation of abrocitinib,
- Indicators of adherence to performing laboratory tests of CBC and lipid panel at Week 4 (± 2 weeks) from initiation of abrocitinib treatment,
- Indicators of adherence to consideration of risk factors for thrombotic events including pulmonary embolism prior to treatment with abrocitinib,
- Indicators of adherence to avoid live attenuated vaccine immediately prior to and during treatment with abrocitinib,
- Indicators of adherence to contraindications for use during pregnancy, and
- Indicators of adherence to not use in patients aged <18 years of age.

Study B7451015: A Phase 3 Multi-Center, Long-Term Extension Study Investigating the Efficacy and Safety of Abrocitinib, With or Without Topical Medications, Administered to Subjects Aged 12 Years and Older with Moderate to Severe Atopic Dermatitis

Purpose of the Study:

The objective of this study is to assess the long-term safety of 100 mg and 200 mg once daily of abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials.

The study objectives will be to assess safety by the spontaneous reporting of AEs, physical examinations and clinical laboratory results in all subjects who receive at least one dose of the investigational product. This study will continue to describe safety data to include:

- Thrombotic events including pulmonary embolism,
- Serious and opportunistic infections,
- Herpes zoster,
- Malignancy,
- Fracture, including in adolescents,
- Myopathy (including rhabdomyolysis),
- Gastrointestinal perforation,
- MACE,
- Height in adolescents,
- Development in adolescents and
- Pregnancy outcomes.

B7451015: Adolescent Imaging Substudy

Purpose of the Substudy

The objective of this substudy is to evaluate the potential effects of abrocitinib in terms of abnormal bone findings in knee MRI in subjects enrolled as adolescents (12 to <18 years of age) in the abrocitinib development program. The substudy will evaluate the proportion of abnormal bone finding in knee MRI in adolescent subjects exposed to abrocitinib 100 mg and 200 mg QD.