PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

LITFULO (Ritlecitinib)

Marketing Authorization Number 69695

Hard capsules, 50 mg

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LIST OF ABBREVIATIONS

AA	Alopecia areata
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
MACE	Major Adverse Cardiac Event
PL	Package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics (Europe)

OVERVIEW

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 minimise them. The RMP summary for Litfulo 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 médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Litfulo in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of Litfulo.

SUMMARY OF RISK MANAGEMENT PLAN FOR LITFULO (RITLECITINIB)

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

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

This summary of the RMP for Litfulo 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 Litfulo's RMP.

I. The Medicine and What It Is Used For

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older. It contains Ritlecitinib as the active substance and it is given by oral of administration.

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

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

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

In addition to these measures, information about adverse events is 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 Litfulo is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Litfulo 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 Litfulo 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 (eg on the long-term use of the medicine).

Table 1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Herpes zoster
Important potential risks	Serious and Opportunistic Infections
	Malignancy
	Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis
	Embryofoetal toxicity following exposure in utero
	MACE
	Neurotoxicity
Missing information	Long -Term Safety
	Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development.

II.B Summary of Important Risks

Table 2. Important Identified Risk: Herpes Zoster

Evidence for linking the risk to the medicine	Clinical study data of Ritlecitinib and understanding of effects of immunomodulatory mechanisms. Herpes zoster infections were assessed in the Ritlecitinib development program.
Risk factors and risk groups	Risk factors for Herpes zoster infections include patients that use drugs along with Ritlecitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts and people with weakened immune systems.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special warnings and precautions for use. SmPC Section 4.8 Undesirable Effects Additional risk minimisation measures Healthcare Professional Guide Patient Card

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Drug utilization study B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 3. Important Potential Risk: Serious and Opportunistic infections

Evidence for linking the risk to the medicine	Clinical study data of Ritlecitinib and understanding of immunomodulatory mechanisms. Serious infections and adjudicated opportunistic infections were assessed in the Ritlecitinib development program.
Risk factors and risk groups	Risk factors for serious infections include elderly age, certain medical conditions such as diabetes, patients that use drugs along with Ritlecitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts and people with weakened immune systems.
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 Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Drug utilization study B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 4. Important Potential Risk: Malignancy

Evidence for linking the risk to the medicine	Clinical study data and understanding of immunomodulatory mechanisms based on the data from the JAK class. Adjudicated malignancy events were assessed in the Ritlecitinib development program.
Risk factors and risk groups	Malignancies were observed in clinical studies of Ritlecitinib. However, there were an insufficient number of events for risk factor or subgroup analysis. The risks and benefits of Ritlecitinib treatment should be considered prior to initiating or continuing therapy in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer (NMSC) or cervical cancer).
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special Warnings and Precautions for use Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Drug utilization study B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 5. Important Potential Risk: Thromboembolic events including deep vein thrombosis, pulmonary embolism and arterial thrombosis

Evidence for linking the risk to the medicine	Thrombotic events have been reported in patients receiving Ritlecitinib in clinical studies. Adjudicated thromboembolic events (venous and arterial) were assessed in the Ritlecitinib development program.
Risk factors and risk groups	There were an insufficient number of cases to analyze risk factors from the Ritlecitinib clinical trial data. Risk factors for thromboembolic events in the general population also apply to patients with AA including older age, obesity, a medical history of thromboembolism, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 Special Warnings and Precautions for use Additional risk minimisation measures Healthcare Professional Guide Patient card

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Drug utilization study B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 6. Important Potential Risk: Embryofoetal toxicity following exposure in utero

Evidence for linking the risk to the medicine	There are limited data from the use of Ritlecitinib in human pregnancy. Studies in animals have shown developmental toxicity with no effects at clinically relevant exposures. In an embryo-foetal development study in pregnant rats, oral administration of Ritlecitinib from gestation days 6 to 17 resulted in foetal skeletal malformations and variations and lower foetal body weights at exposures greater than or equal to 49 times the unbound AUC at the MRHD. There were no effects on embryo-foetal development at exposures equal to 16 times the unbound AUC at the MRHD. In an embryo-foetal development study in pregnant rabbits, oral administration of Ritlecitinib from gestation days 7 to 19 resulted in lower mean foetal body weights and higher incidences of visceral malformations, skeletal malformations, and skeletal variations at exposures equal to 55 times the unbound AUC at the MRHD. There were no effects on embryo-foetal development at exposures equal to 12 times the unbound AUC at the MRHD. In a rat pre- and postnatal development study, oral administration of Ritlecitinib from gestation day 6 through lactation day 20 resulted in developmental toxicity that included lower postnatal survival, lower offspring body weights, and secondary developmental delays at exposure equal to 41 times the unbound AUC at the MRHD. Bred females in the F1 generation exhibited lower mean numbers of corpora lutea at exposures equal to 41 times the unbound AUC at the MRHD. There were no effects on pre- and postnatal development at exposures equal to 14 times the unbound AUC at the MRHD.
Risk factors and risk groups	Risk of foetal malformation pertains only to women of childbearing potential who become pregnant while receiving Ritlecitinib. There were no cases reported of Embryofoetal toxicity.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy and lactation. Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Drug utilization study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 7. Important Potential Risk: MACE

Evidence for linking the risk to the medicine	Events of venous and arterial thromboembolism including MACE, have been reported in patients receiving Ritlecitinib. It is not known whether JAK3 inhibition may be associated with all adverse reactions of non-selective JAK inhibition. In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in RA patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, and a dose dependent higher rate of venous thromboembolism including DVT and PE were observed with a JAK inhibitor compared to TNF inhibitors.
Risk factors and risk groups	There was an insufficient number of events in the Ritlecitinib development program for formal risk factor or subgroup analysis. Age ≥65 years, current or past smoking history, and a history of atherosclerotic disease are risk factors for MACE in patients treated with JAK class inhibitors.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special Warnings and Precautions for use Additional risk minimisation measures Healthcare Professional Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 8. Important Potential Risk: Neurotoxicity

Evidence for linking the risk to the medicine	Ritlecitinib-related axonal dystrophy has been observed in chronic Beagle dog toxicity studies (see section 5.3). Treatment with Ritlecitinib should be discontinued in case unexplained neurological symptoms occur.
Risk factors and risk groups	Risk factors in the general population include extremes in age, prior neurological disease, chronic illness and renal impairment.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.4 Special Warnings and Precautions for use SmPC Section 5.3 Pre-clinical Safety Data Additional risk minimisation measure Healthcare Professional Guide Patient Card

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Active surveillance study in adolescents (primary data collection) B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 9. Missing Information: Long-Term Safety

Evidence for linking the risk to the medicine	There are limited long-term safety data from Ritlecitinib clinical studies.
Risk Minimisation Measures	Routine risk minimisation measures: None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Active surveillance study in adolescents (primary data collection) B7981032 Long-term study See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 10. Missing Information: Long-Term safety in adolescent patients including growth and bone development, and maturation and pubertal development.

Evidence for linking the risk to the medicine	There were limited long-term data in adolescent participants in clinical studies to fully characterize any potential effect on growth and bone development, and maturation and pubertal development.
Risk Minimisation Measures	Routine risk minimisation measures: None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Active surveillance study in secondary databases Active surveillance study in adolescents (primary data collection) B7981032 Long-term 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

The following studies are conditions of the marketing authorisation:

None.

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

Plan Study short name

An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Europe (Secondary Databases) (See RMP Part VII Annex 3 for protocol synopsis)**.**

Purpose of the study: The primary objective is to estimate the incidence rates (IRs) of safety events of interest among patients with AA receiving Ritlecitinib and patients with AA receiving other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest:

- Thromboembolic events (including deep vein thrombosis [DVT], pulmonary embolism [PE], and arterial thrombosis);
- Herpes zoster;
- Serious infections;
- Opportunistic infections;
- Malignancy;
    - Malignancy excluding nonmelanoma skin cancer (NMSC); and
    - NMSC.
- Major adverse cardiovascular events (MACE);
- Neurological events of interest;
- Bone fractures; and
- Growth metrics in adolescents (e.g., height and weight; Denmark only).

Other safety events may be added as understanding of the safety profile of Ritlecitinib evolves and feasibility of their assessment permits.

Study short name

A Drug Utilization Study to Evaluate the Effectiveness of Risk Minimization Measures for Ritlecitinib in Europe Using Electronic Healthcare Data (See RMP Part VII Annex 3 for protocol synopsis).

Purpose of the study:

To evaluate, to the extent measurable in the available routinely collected data, indicators of healthcare professional's (HCPs) adherence to the risk minimization measures (RMMs) in accordance with the Ritlecitinib Summary of Product Characteristics (SmPC), HCP guide, and Patient Card.

Describe the characteristics of patients prior to initiation of Ritlecitinib treatment.

Study short name

A Prospective Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Adolescents with Alopecia Areata (Primary Data Collection) (See RMP Part VII Annex 3 for protocol synopsis).

Purpose of the study:

The primary objectives are to:

- Describe growth and bone development metrics among adolescent patients

treated with Ritlecitinib and, separately, among adolescent patients with AA who are unexposed to Ritlecitinib, including those exposed to other approved systemic treatments for AA;

- Describe maturation and pubertal development metrics among adolescent patients treated with Ritlecitinib and, separately, among adolescent patients with AA who are unexposed to Ritlecitinib, including those exposed to other approved systemic treatments for AA; and

- Estimate the incidence rate of neurological events of interest among adolescent patients treated with Ritlecitinib and, separately, among adolescent patients with AA who are unexposed to Ritlecitinib, including those exposed to other approved systemic treatments for AA.

Exploratory objectives are to:

- Compare growth and bone development metrics among adolescent patients treated with Ritlecitinib with adolescent patients with AA who are unexposed to Ritlecitinib, including those exposed to other approved systemic treatments for AA;

- Compare maturation and pubertal development metrics among adolescent patients treated with Ritlecitinib with adolescent patients with AA who are unexposed to Ritlecitinib, including those exposed to other approved systemic treatments for AA; and
- Compare the incidence rate of neurological events of interest among adolescent patients treated with Ritlecitinib to the incidence rate among adolescent patients with AA who are unexposed to Ritlecitinib, including those exposed to other approved systemic treatments for AA.

B7981032 Long-term study

Study short name:

Long-Term Study Evaluating Ritlecitinib in Adults and Adolescents with Alopecia Areata (See RMP Part VII Annex 3 for protocol amendment 6).

Rationale and Study Objectives

This study is specifically designed to evaluate the long-term safety, tolerability and efficacy of Ritlecitinib in adults and adolescents.

The primary objectives are:

- To evaluate the long-term safety and tolerability of Ritlecitinib in adult and adolescent participants with AA.

The secondary objectives are:

- To evaluate the effect of Ritlecitinib on participant-centered outcomes and payer relevant measures to assess treatment benefit from the participant perspective and to demonstrate value.

- To evaluate the long-term efficacy of Ritlecitinib in adult and adolescent participants with AA.