swissmedic

Date: 17 April 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Litfulo

International non-proprietary name:	ritlecitinib
Pharmaceutical form:	hard capsule
Dosage strength(s):	50 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Pfizer AG
Marketing authorisation no.:	69695
Decision and decision date:	approved on 3 February 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

AA	Alopecia areata
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AT	Alopecia totalis
AU	Alopecia universalis
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IR	Immediate release
ITT	Intention-to-treat
JAK	Janus Kinase
JAKi	Janus Kinase inhibitor
LDPE	Low density polyethylene
LoQ	List of Questions
MACE	Major adverse cardiac events
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NMSC	Non-melanoma skin cancer
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PY	Person-years
QD	Once daily
QTPP	Quality target product profile
RMP	Risk management plan

SAE	Serious adverse event
SALT	Severity of Alopecia Tool
SMC	Swissmedic
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for ritlecitinib in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see «Properties/Effects»).

2.2.2 Approved indication

Litfulo is indicated for the treatment of severe alopecia areata (≥50% of the scalp affected) in adults up to a maximum of 65 years of age and adolescents 12 years of age and older who are eligible for systemic therapy (see «Properties/Effects, Clinical Efficacy»).

2.2.3 Requested dosage

The recommended dose is 50 mg once daily.
The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis. Consideration should be given to discontinuing patients who show no evidence of therapeutic benefit after 36 weeks.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	4 December 2023
Formal control completed	28 December 2023
List of Questions (LoQ)	25 April 2024
Response to LoQ	12 July 2024
Preliminary decision	10 October 2024
Response to preliminary decision	5 November 2024
Final decision	3 February 2025
Decision	approval

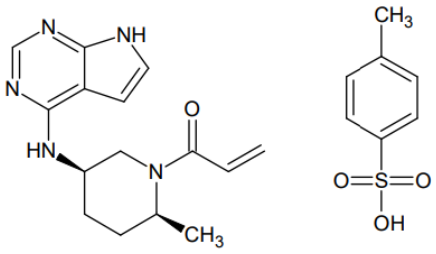
3 Medical context

Alopecia areata is a chronic, immune-mediated, non-lethal disorder targeting anagen hair follicles leading to non-scarring, patchy, circular hair loss, preferentially at the scalp. Up to 10% of patients experience a total hair loss on the scalp (alopecia totalis (AT)), or on the whole body (alopecia universalis (AU)). The severity of the scalp hair loss is documented by the Severity of Alopecia Tool (SALT) score, which ranges from 0 (no bald spots) to 100 (100% hair loss). Conventionally, ≥50% hair loss (i.e., SALT ≥50) is referred to as severe alopecia, ≥95% hair loss (i.e. SALT ≥95) is referred to as very severe alopecia.
The lifetime risk (incidence proportion when the given period of time is the entire lifetime) is approximately 2%, both genders are affected equally, and the patients are typically of younger age. Around 50% of patients with limited patchy hair loss recover within a year, although several episodes in a lifetime are common. Although the disease is non-lethal, the stigmatizing effect may have significant psychological impact.
Available therapeutic options are locally applied and/or intralesionally injected corticosteroids, systemic immunosuppressants (e.g. methotrexate, oral corticosteroids), and/or cover-ups (i.e. wigs). All currently available non-Janus kinase inhibitors (non-JAKi) therapies show an unsatisfactory response and high relapse rates. Since 2023, the JAK inhibitor baricitinib has been approved in Switzerland for the treatment of severe alopecia areata in adults. Given that ritlecitinib is submitted for the treatment of adolescents as well, and since the therapeutic options are very limited, there is a clear unmet medical need despite the fact that alopecia areata is a non-lethal condition per se.

4 Quality aspects

4.1 Drug substance

Drug Substance

INN:	Ritlecitinib
Chemical name:	1-{(2S,5R)-2-Methyl-5-[(7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}prop-2-en-1-one 4-methylbenzene-1-sulfonic acid (1:1)
Molecular formula:	Free base: $C_{15}H_{19}N_5O$
Molecular mass:	Free base: 285.35 Daltons (Da.) Tosylate salt: 457.55 Daltons (Da.)
Molecular structure:	

Physicochemical properties: Ritlecitinib tosylate is a white to off white to pale pink solid. Ritlecitinib tosylate has two asymmetric centres and is manufactured as a single stereoisomer. The compound is considered highly soluble in the biopharmaceutical classification system.

Synthesis: The synthesis of ritlecitinib tosylate consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials critical steps and intermediates.

Specification: The drug substance specification includes tests for appearance, identity, chiral identification, assay, impurities, water content, residual solvents, counter ion, residue on ignition and particle size distribution. The applied limits are justified and in line with the relevant guidelines and the European Pharmacopoeia, if applicable. The analytical methods are adequately described and validated in accordance with the ICH guidelines.

Stability: The bulk drug substance is packaged in Low Density Polyethylene (LDPE) bags. A stability study was carried out according to the current guideline recommendations. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug product

Description and composition: Ritlecitinib drug product is provided as an immediate-release (IR) opaque hard capsule manufactured from a common blend in the 50 mg strength (size #3, yellow body/blue cap). The body is printed with “RCB 50” and the cap is printed with “Pfizer” in black. In addition to the active ingredient ritlecitinib tosylate, the capsules contain the pharmaceutical excipients cellulose microcrystalline, lactose monohydrate, crospovidone, and glycerol dibehenate. The capsule shells consist of hypromellose (E 464), titanium dioxide (E 171), yellow iron oxide (E172), and brilliant blue (E133). The printing ink present on the capsule contains shellac, propylene glycol, ammonia solution concentrated, black iron oxide (E172), and potassium hydroxide.

Pharmaceutical development: The formulation and process development of ritlecitinib capsules focused on the quality attributes defined in the Quality Target Product Profile (QTPP). An enhanced development programme was executed in accordance with ICH Guideline Q8. A combination of risk-based assessments, small scale multivariate studies, and manufacturing experience at the proposed commercial manufacturing site has resulted in a comprehensive understanding of the formulation and process conditions and their impact on the quality attributes of the ritlecitinib drug product.

Manufacture: Ritlecitinib capsules are manufactured by a standard manufacturing process which includes blending, screening and encapsulation using commonly available equipment in the pharmaceutical industry.

Specification: The drug product specifications include tests for appearance, identity, assay, degradation products, dissolution, uniformity of dosage units, water activity and microbial purity. The proposed acceptance criteria and analytical methods were considered appropriate for the quality control of the drug product.

Container closure system: The capsules are packaged into aluminium foil blisters with aluminium foil lidding.

Stability: Appropriate stability data are provided for ritlecitinib capsules. The stability studies were carried out according to ICH stability guidelines. Based on the results of the studies, an appropriate shelf-life was established.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application of ritlecitinib, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the European Medicines Agency (EMA) assessment report (EMA/CHMP/232413/2023) dated 20.07.2023 and provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of ritlecitinib in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues regarding neurological findings, reproductive/developmental toxicity, and carcinogenicity identified in non-clinical studies that would be of concern for human use are addressed in both the Information for healthcare professionals and the RMP. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and the US FDA. The available assessment reports and the Summary of Product Characteristics from the EMA and the Prescribing Information from the US FDA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, please see section 8 of this report.

6.2 Dose finding and dose recommendation

Swissmedic has assessed the primary data relating to the clinical aspects submitted with this application in addition to the Assessment Reports of the EMA and FDA. This is due to the fact that ritlecitinib belongs to the JAK inhibitor family, and the safety measures implemented for this class of drugs, including labelling and boxed warnings, differ between agencies (FDA, EMA and Swissmedic (SMC)).

Dose-response has been studied in the pivotal phase 2b/3 study (B7981015). Instead of a dose-response study, the pivotal study was preceded by a phase 2a proof-of-concept study (B7931005), which investigated ritlecitinib in a single-dose regimen with a loading dose of 200 mg, followed by 50 mg QD (200/50 mg QD) in comparison to placebo. Based on data from both studies it was agreed that 50 mg without a loading dose was an effective alternative to the maximal dosing regimen: 200/50 mg. The beneficial effect of an additional loading dose was only given for the first 24 weeks of treatment, but neglectable for a treatment up to 48 weeks. Since the latter was considered clinically more relevant; therefore, it was reasonable to exclude the loading dose.

6.3 Efficacy

One pivotal study was submitted (B7981015). Given the large sample size, the methodologically adequate design, the well-chosen endpoints, the statistically significant and consistent results in the relevant endpoints, and the submitted supportive data, this is considered acceptable. The pivotal study demonstrated a statistically significant and clinically relevant benefit of ritlecitinib 50 mg QD compared to placebo in regard to achieving a SALT score ≤10 (13.4% vs 1.5%) at week 24. Also, a SALT score ≤20 was more likely to be achieved in the ritlecitinib 50 mg QD arm compared to placebo (23.4% vs 1.5%). Further, the response in terms of the Patient Global Impression of Change (PGI-C) score (the proportion of patients who documented ‘moderately improved’ or ‘greatly improved’ in PGI-C score) was more likely to be achieved in the ritlecitinib 50 mg QD arm compared to placebo (49.2% vs 9.2%) at week 24.
From week 24 to 48, the proportion of patients that responded to ritlecitinib therapy (achieving SALT ≤10, PGI-C or SALT ≤20) further increased. These findings are supported by the results in regard to regrowth of eyebrows and eyelashes, and by the patient-reported impression of improvement.

However, no statistically significant difference between ritlecitinib and placebo was seen in the subgroup of patients without a prior treatment for alopecia areata. For this sub-group, data submitted as response to LoQ based on a longer observation period showed slower, albeit positive, SALT ≤10 responses, with decreasing difference between the sub-groups after 48 weeks. Therefore, the objection regarding prior therapy is partially resolved taking also the following facts into the consideration:

- the sub-groups differed regarding baseline parameters, which may have affected efficacy (e.g. higher percentage of patients with AT/AU in the sub-group w/o prior therapy),

- applied prior therapies were off-label, and thus with unconfirmed efficacy, in severe AA
- the disease has typically a progressive course, making application of topical treatments more useful for less advanced disease.

Because of potential lifelong therapy with potential significant risks, the positive benefit-risk in treatment-naïve patients was endorsed under the provision that the indication was restricted to patients who are candidates for systemic therapy.

Also, no statistically significant difference between ritlecitinib and placebo was seen in the subgroup of patients aged 65 years and older. Scarce efficacy data were supported by the results of the PK modelling. Although age was not identified as an important covariate, the PK results are of limited value, as they are based on a small number of samples that were obtained under different dosing regimens.

6.4 Safety

At initial submission, a total of 1521 patients (1763 PY) were exposed to ritlecitinib 50 mg QD or higher, with 1011 patients experiencing at least 12 months of exposure. 172 patients were adolescents (age 12 to 17), of whom 133 patients were exposed for at least 12 months. In its response to LoQ, the applicant submitted an updated safety report with the data cut-off of 9.12.2022. This included:

- 1523 patients and 2461 PYs exposed to ritlecitinib 50 mg or higher
- 1630 patients and 2782 PYs exposed to any ritlecitinib dose

In this report, data for up to 3 years of treatment were available based on 214 patients exposed to 50 mg and 356 patients exposed to any dose.

In the placebo-controlled pool with a 24-week treatment period, common adverse events that were more frequently reported in the ritlecitinib arm compared to the placebo arm included: nasopharyngitis, diarrhoea, headache, acne, urticaria, rash, upper abdominal pain, pyrexia, folliculitis, COVID-19, dizziness, and atopic dermatitis. These findings were similar in the one-year exposure pool. Overall, 2 deaths were reported in the study programme, both in the all-exposure pool. Major adverse cardiac events (MACE), serious infections, malignancies, and non-melanoma skin cancer (NMSC) were infrequently reported. However, in this relatively young population, the observation period may be too short to allow for significant numbers of manifestations of these long-term adverse events. Thus, it remains unclear whether ritlecitinib inherits a JAK inhibitor family-like risk for these adverse events.

The safety profile in adolescents was similar compared to adults. Measurements of height and weight did not imply any deviations from normal growth within the limited observation time. Elderly patients (>65 years of age) were more likely than adults to experience severe adverse events, serious adverse events, and adverse events leading to permanent discontinuation. Even though the sample size was very small, these findings were considered relevant in the light of large uncertainties in regard to efficacy, leading to a negative benefit-risk analysis in the elderly.

6.5 Final clinical benefit risk assessment

Submitted data demonstrated a statistically significant and clinically relevant beneficial effect of ritlecitinib compared to placebo in the treatment of severe alopecia areata in adolescents 12 years of age and older and adults up to 64 years of age. The safety profile was acceptable overall, yet relevant uncertainties in regard to the long-term safety remained. Therefore, the indication was restricted to adolescents of at least 12 years and adults up to 65 years of age, who are candidates for systemic therapy and JAKi-specific labelling measures, including a black box warning, were implemented.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Litfulo was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

IMPORTANT WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCIES, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

- **Increased risk of serious** bacterial, fungal, viral, and opportunistic **infections** leading to hospitalization or death, including tuberculosis (TB). Discontinue treatment with Litfulo if a serious infection occurs until the infection is controlled.
- **Higher rate of overall mortality**, including sudden cardiovascular death with another Janus Kinase (JAK) inhibitor compared with tumour necrosis factor (TNF) inhibitors in patients with rheumatoid arthritis (RA).
- **Malignancies** have occurred in patients treated with Litfulo. Higher rates of **lymphomas** and **lung cancer** with another JAK inhibitor compared with TNF inhibitors in RA patients.
- **Higher rate of MACE** (defined as **cardiovascular death, myocardial infarction, and stroke**) with another JAK inhibitor compared with TNF inhibitors in RA patients.
- **Thromboembolic events** have occurred in patients treated with Litfulo. Increased incidence of **pulmonary embolism**, **venous** and **arterial thrombosis** with another JAK inhibitor compared with TNF inhibitors.

For more information, please consult the «Warnings and Precautions» section.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Litfulo

Composition

Active substances

Ritlecitinibum (ut Ritlecitinibi Tosilas).

Excipients

Hard capsule content: Cellulosum microcristallinum, lactosum monohydricum (21.27 mg), crospovidonum, glyceroli dibehenas.

Hard capsule shell: Hypromellosum (E 464), titanii dioxidum (E 171), ferrum oxydatum flavum (E 172), Brilliant Blue (E 133).

Printing ink: Lacca, propylenglycolum, ammoniae solutio concentrata, ferrum oxydatum nigrum (E 172), kalii hydroxidum.

Pharmaceutical form and active substance quantity per unit

Hard capsule (capsule) containing 50 mg ritlecitinib.

Opaque hard capsules, yellow body and blue cap approximately 16 mm long and 6 mm wide, of which the body is printed with «RCB 50» and the cap is printed with «Pfizer» in black.

Indications/Uses

Litfulo is indicated for the treatment of severe alopecia areata (≥50% of the scalp affected) in adults up to a maximum of 65 years of age and adolescents 12 years of age and older who are eligible for systemic therapy (see «Properties/Effects, Clinical Efficacy»).

Dosage/Administration

Treatment should be initiated and supervised by dermatologists experienced in the diagnosis and treatment of alopecia areata according to individual risk-benefit assessment (see «Warnings and precautions»).

Posology

The recommended dose is 50 mg once daily.

The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis.

Consideration should be given to discontinuing patients who show no evidence of therapeutic benefit (at least 30% improvement in SALT-score) after 36 weeks.

The combination with biological immunomodulators, other JAK inhibitors, ciclosporin or other strong immunosuppressants has not been studied and is not recommended.

Laboratory monitoring

Table 1: Laboratory measures and monitoring guidance

Laboratory measures	*Monitoring guidance*	*Action*
Platelet count	Before treatment initiation, 4 weeks after initiation, and thereafter according to routine patient management.	Treatment should be discontinued if platelet count is $<50 \times 10^3/mm^3$.
Lymphocytes		Treatment should be interrupted if ALC is $<0.5 \times 10^3/mm^3$ and may be restarted once ALC return above this value.

Abbreviation: ALC = absolute lymphocyte count

Treatment initiation

Treatment with ritlecitinib should not be initiated in patients with an absolute lymphocyte count (ALC) $<0.5 \times 10^3/mm^3$ or a platelet count $<100 \times 10^3/mm^3$ (see «Warnings and precautions»).

Treatment interruption or discontinuation

If a patient develops a serious infection or opportunistic infection, ritlecitinib should be interrupted until the infection is controlled (see «Warnings and precautions»).

Interruption or discontinuation of treatment may be needed for management of haematologic abnormalities as described in Table 1.

If treatment interruption is needed, the risk of significant loss of regrown scalp hair after a temporary treatment interruption for less than 6 weeks is low.

Missed doses

If a dose is missed, patients should be advised to take the dose as soon as possible unless it is less than 8 hours before the next dose, in which case the patient should not take the missed dose. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment (see «Pharmacokinetics»).

Ritlecitinib has not been studied in patients with end-stage renal disease (ESRD) or in patients with renal transplants and is therefore not recommended for use in these patients.

Hepatic impairment

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see). Ritlecitinib is contraindicated in patients with severe (Child Pugh C) hepatic impairment (see «Contraindications»).

Elderly

Clinical experience in patients over 65 years of age is very limited and therefore these patients should not be treated with ritlecitinib.

Paediatric population

No dose adjustment is required for adolescents 12 to <18 years of age.

The safety and efficacy of Litfulo in children under 12 years of age have not yet been established. No data are available.

Method of administration

Litfulo is to be taken once daily with or without food.

Capsules should be swallowed whole and should not be crushed, split or chewed, because these methods of administration have not been studied in clinical trials.

Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in «Composition».
- Active serious infections, including tuberculosis (TB) (see «Warnings and precautions»).
- Severe hepatic impairment (see «Dosage/Administration»).
- Pregnancy and breast-feeding (see «Pregnancy, lactation»).

Warnings and precautions

Serious infections

Serious infections have been reported in patients receiving ritlecitinib. The most frequent serious infections have been appendicitis, COVID-19 infection (including pneumonia), and sepsis. Treatment with ritlecitinib must not be initiated in patients with an active, serious infection (see «Contraindications»).

The risks and benefits of treatment should be considered in patients:

- with chronic or recurrent infection.
- who have been exposed to tuberculosis (TB).
- with a history of serious or an opportunistic infection.
- who have resided or traveled in areas of endemic TB or mycoses, or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ritlecitinib. Treatment should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with ritlecitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. If interrupted, ritlecitinib may be resumed once the infection is controlled.

As there is a higher incidence of infections in elderly and in the diabetic population in general, caution should be exercised when treating the elderly and patients with diabetes, and particular attention paid with respect to occurrence of infections.

Tuberculosis

Patients should be screened for TB before starting therapy with ritlecitinib. Ritlecitinib must not be given to patients with active TB (see «Contraindications»). Anti-TB therapy should be started prior to initiating therapy with ritlecitinib in patients with a new diagnosis of latent TB or previously untreated latent TB. In patients with a negative latent TB test, anti-TB therapy should still be considered before initiating treatment with ritlecitinib in those at high risk and screening for patients at high risk for TB during treatment with ritlecitinib should be considered.

Viral reactivation

Viral reactivations, including cases of herpes virus reactivation (e.g., herpes zoster), have been reported (see «Undesirable effects»). If a patient develops herpes zoster, temporary interruption of treatment may be considered until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with ritlecitinib. Patients with evidence of hepatitis B or C infection were excluded from studies with ritlecitinib. Monitoring for reactivation of viral hepatitis according to clinical guidelines is recommended during ritlecitinib treatment. If there is evidence of reactivation, a liver specialist should be consulted.

Overall Mortality

In a large, randomized safety study conducted after the market introduction of another JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher overall mortality rate, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared to patients treated with TNF inhibitors. Ritlecitinib is not indicated for RA. Before starting or continuing therapy with ritlecitinib, weigh the benefits and risks for the individual patient.

Malignancy (including non-melanoma skin cancer)

Malignancies, including non-melanoma skin cancer (NMSC) have been reported in patients receiving ritlecitinib.

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 malignancies, particularly lung cancer, lymphoma and NMSC, was observed with tofacitinib compared to tumour necrosis factor (TNF) inhibitors. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF inhibitors. In this study, current or past smokers had an additional increased risk of overall malignancies.

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 NMSC or cervical cancer.

Periodic skin examination is recommended for patients who are at increased risk of skin cancer.

Major adverse cardiovascular events (MACE), deep venous thrombosis (DVT) and pulmonary embolism (PE)

Events of venous and arterial thromboembolism, including MACE, have been reported in patients receiving ritlecitinib.

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 dosedependent higher rate of venous thromboembolism including DVT and PE were observed with tofacitinib compared to TNF inhibitors. Patients who are current or past smokers were at additional increased risk.

Ritlecitinib should be used with caution in patients with known risk factors for thromboembolism. In patients with a suspected thromboembolic event, discontinuation of ritlecitinib and prompt re-evaluation is recommended. The risks and benefits of ritlecitinib treatment should be considered prior to initiating therapy in patients, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors.

Neurological events

Ritlecitinib-related axonal dystrophy has been observed in chronic Beagle dog toxicity studies (see «Preclinical data»). Treatment with ritlecitinib should be discontinued in case unexplained neurological symptoms occur.

Haematologic abnormalities

Treatment with ritlecitinib was associated with decreases in lymphocytes and platelets (see «Undesirable effects»). Prior to initiating treatment with ritlecitinib, ALC and platelet counts should be performed. Treatment with ritlecitinib should not be initiated in patients with an ALC $<0.5 \times 10^3/mm^3$ or a platelet count $<100 \times 10^3/mm^3$. After initiating treatment with ritlecitinib, treatment interruption or discontinuation are recommended based on ALC and platelet count abnormalities (see «Dosage/Administration»). ALC and platelet counts are recommended at 4 weeks after initiation of therapy with ritlecitinib, and thereafter according to routine patient management.

Vaccinations

No data are available on the response to vaccination in patients receiving ritlecitinib. Use of live attenuated vaccines should be avoided during or immediately prior to ritlecitinib treatment. Prior to

initiating ritlecitinib, it is recommended that patients are brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines.

Elderly

Clinical experience in patients ≥65 years of age is very limited and therefore these patients should not be treated with ritlecitinib.

Excipients of particular interest

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interactions

Effect of other agents on the pharmacokinetics of ritlecitinib

Other interactions

The metabolism of ritlecitinib is mediated by multiple pathways, with no single clearance route contributing more than 25% (see «Pharmacokinetics»). Hence, medicinal products inhibiting a selective metabolic pathway are unlikely to impact the systemic exposures of ritlecitinib. Specific inhibitors of transporters are unlikely to result in clinically relevant changes in the bioavailability of ritlecitinib.

CYP3A inhibitors: the coadministration of multiple 200 mg doses of itraconazole, a strong CYP3A inhibitor, increased the area under curve $(AUC)_{inf}$ of ritlecitinib by approximately 15%. This is not considered clinically significant and, therefore dose adjustment is not required when ritlecitinib is coadministered with CYP3A inhibitors.

CYP inducers: the coadministration of multiple 600 mg doses of rifampicin, a strong inducer of CYP enzymes, decreased the AUC_{inf} of ritlecitinib by approximately 44%. This is not considered clinically significant and, therefore dose adjustment is not required when ritlecitinib is coadministered with inducers of CYP enzymes.

In vitro, ritlecitinib is a substrate of P-glycoprotein (P-gp) and BCRP. However, as ritlecitinib has a high fraction absorbed (f_a) with both C_{max} and AUC increases in a dose proportional manner (20-200 mg single dose range), P-gp and BCRP are not expected to have a meaningful impact on the absorption of ritlecitinib.

Effect of ritlecitinib on the pharmacokinetics of other agents

Other interactions

Ritlecitinib is a covalent inhibitor that has been shown to bind to off-target proteins such as MAP2K7, DOCK10, albumin, CYP1A2, CYP3A, UGT1A1, and UGT1A4, some of which may have clinical relevance in drug interactions.

CYP3A substrates: multiple doses of 200 mg once daily ritlecitinib increased the AUC_{inf} and C_{max} of midazolam a CYP3A4 substrate, by approximately 2.7-fold and 1.8-fold, respectively. Ritlecitinib is a moderate inhibitor of CYP3A; caution should be exercised with concomitant use of ritlecitinib with CYP3A substrates (e.g., quinidine, cyclosporine, dihydroergotamine, ergotamine, pimozide) where moderate concentration changes may lead to serious adverse reactions. Dose adjustment recommendations for the CYP3A substrate (e.g., colchicine, everolimus, tacrolimus, sirolimus) should be considered.

CYP1A2 substrates: multiple doses of 200 mg once daily ritlecitinib increased the AUC_{inf} and C_{max} of caffeine, a CYP1A2 substrate, by approximately 2.7-fold and 1.1-fold, respectively. Ritlecitinib is a moderate inhibitor of CYP1A2; caution should be exercised with concomitant use of ritlecitinib with other CYP1A2 substrates (e.g., tizanidine) where moderate concentration changes may lead to serious adverse reactions. Dose adjustment recommendations for the CYP1A2 substrate (e.g., theophylline, pirfenidone) should be considered.

OCT1 substrates: the coadministration of a single 400 mg dose of ritlecitinib increased the AUC_{inf} of sumatriptan (an organic cation transporter [OCT]1 substrate) by approximately 1.3 to 1.5-fold relative to sumatriptan dose given alone. The increase in sumatriptan exposure is not considered clinically relevant. Caution should be exercised with concomitant use of ritlecitinib with OCT1 substrates where small concentration changes may lead to serious adverse reactions.

Ritlecitinib did not produce clinically significant changes in the exposures of oral contraceptives (e.g., ethinyl oestradiol or levonorgestrel), CYP2B6 substrates (e.g., efavirenz), CYP2C substrates (e.g., tolbutamide), or substrates of organic anion transporter (OAT)P1B1, breast cancer resistant protein (BCRP), and OAT3 (e.g., rosuvastatin).

Paediatric population

Interaction studies have only been performed in adults.

Pregnancy, lactation

Women of childbearing potential

Ritlecitinib is not recommended in women of childbearing potential not using contraception. Women of childbearing potential have to use effective contraception during treatment and for 1 month following the final dose of Litfulo.

Pregnancy

There are no or limited data from the use of ritlecitinib in pregnant women. Studies in animals have shown reproductive toxicity (see «Preclinical data»). Litfulo is contraindicated during pregnancy (see «Contraindications»).

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of ritlecitinib in milk (see «Preclinical data»). A risk to newborns/infants cannot be excluded. Litfulo is contraindicated during breast-feeding (see «Contraindications»).

Fertility

The effect of ritlecitinib on human fertility has not been evaluated. In animal studies there were no effects on fertility at clinically relevant exposures (see «Preclinical data»).

Effects on ability to drive and use machines

No corresponding studies have been performed. Litfulo can cause dizziness. The clinical condition of the patient and the adverse reaction profile of Litfulo should be considered when assessing the patient's ability to drive or operate machines.

Undesirable effects

Summary of the safety profile

A total of 1630 patients were treated with ritlecitinib representing 2303 patient-years of exposure. Three placebo-controlled studies were integrated (130 participants on 50 mg daily and 213 participants on placebo) to evaluate the safety of ritlecitinib in comparison to placebo for up to 24 weeks after treatment initiation.

The most frequently reported undesirable effects are diarrhoea (9.2%), acne (6.2%), upper respiratory tract infections (6.2%), urticaria (4.6%), rash (3.8%), folliculitis (3.1%), and dizziness (2.3%).

List of adverse reactions

All adverse reactions observed in alopecia areata placebo-controlled studies are presented by system organ class and frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1'000 to <1/100); rare (≥1/10'000 to <1/1'000); very rare (<1/10'000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Common: Herpes zoster, folliculitis, upper respiratory tract infections.

Nervous system disorders

Common: Dizziness.

Gastrointestinal disorders

Common: Diarrhoea.

Skin and subcutaneous tissue disorders

Common: Acne, urticaria, rash.

Investigations

Common: Blood creatine phosphokinase increased.

Uncommon: Platelet count decreased, lymphocyte count decreased, alanine aminotransferase increased >3 × ULN[a], aspartate aminotransferase increased >3 × ULN[a].

[a.] Includes changes detected during laboratory monitoring

Description of selected adverse reactions

Infections

In the placebo-controlled studies, for up to 24 weeks, overall infections have been reported in 31% of patients (80.35 per 100 patient-years) treated with placebo and 33% of patients (74.53 per 100 patient-years) treated with ritlecitinib 50 mg. In study AA-I, for up to 48 weeks, overall infections were reported in 51% of patients (89.32 per 100 patient-years) treated with ritlecitinib 50 mg or higher.

Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, overall infections were reported in 45.4% of patients (50.02 per 100 patient-years) treated with ritlecitinib 50 mg or higher. Most infections were mild or moderate in severity.

In the placebo-controlled studies the percentage of patients reporting infection-related adverse reaction of herpes zoster were 1.5% in the ritlecitinib 50 mg group compared to 0 in placebo. All herpes zoster events were non-serious; 1 patient receiving ritlecitinib 200/50 mg (200 mg once daily for 4 weeks followed by 50 mg once daily) experienced an event of varicella zoster virus infection that met criteria as an opportunistic infection (multi-dermatomal herpes zoster). In study AA-I, for up to 48 weeks, 2.3% of patients (2.61 per 100 patient-years) treated with ritlecitinib 50 mg or higher reported herpes zoster Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, the rate of herpes zoster was 1.10 per 100 patient-years in patients treated with ritlecitinib 50 mg or higher.

In the placebo-controlled studies, for up to 24 weeks, no serious infections were reported in patients treated with placebo or ritlecitinib 50 mg. The proportion and rate of serious infections in patients treated with ritlecitinib 200/50 mg was 0.9% (2.66 per 100 patient-years). In study AA-I, for up to 48 weeks, serious infections were reported in 0.8% of patients (0.86 per 100 patient-years) treated with ritlecitinib 50 mg or higher. Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, the proportion and rate of serious infection in ritlecitinib 50 mg or higher was 0.8% (0.59 per 100 patient-years).

Opportunistic infections

Opportunistic infections of multi-dermatomal herpes zoster were reported in 1 patient (0.50 per 100 patient-years) treated with ritlecitinib 200/50 mg in the placebo-controlled studies, no patients in study AA-I, for up to 48 weeks, and 2 patients (0.09 per 100 patient-years) treated with ritlecitinib 50 mg or higher in the integrated safety analysis, including the long-term study and a study in vitiligo. Cases of opportunistic herpes zoster were mild or moderate in severity.

Decreased lymphocyte count

In the placebo-controlled studies, for up to 24 weeks, and study AA-I, for up to 48 weeks, treatment with ritlecitinib was associated with a decrease in lymphocyte count. Maximum effects on lymphocytes were observed within 4 weeks, after which lymphocyte count remained stable at a lower level with continued therapy. Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, confirmed ALC $<0.5 \times 10^3/mm^3$ occurred in 2 participants (<0.1%) treated with ritlecitinib 50 mg.

Decreased platelet count

In the placebo-controlled studies, for up to 24 weeks, and study AA-I, for up to 48 weeks, treatment with ritlecitinib was associated with a decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which platelet count remained stable at a lower level with continued therapy. Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, 1 patient (<0.1%) treated with ritlecitinib 50 mg or higher had a confirmed platelet count $<100 \times 10^3/mm^3$.

Creatine phosphokinase (CPK) elevations

In the placebo-controlled studies, for up to 24 weeks, events of blood CPK increased were reported in 2 patients (1.5%) treated with ritlecitinib 50 mg. In study AA-I, for up to 48 weeks, events of blood CPK increased were reported in 3.8% of patients treated with ritlecitinib 50 mg or higher. CPK elevations >5x upper limit of normal (ULN) were reported in 2 (0.9%) of patients treated with placebo and 5 (3.9%) of patients treated with ritlecitinib 50 mg. In study AA-I, for up to 48 weeks, CPK elevations >5x ULN were reported in 6.6% of patients treated with ritlecitinib 50 mg or higher. Most elevations were transient and none led to discontinuation.

Increased transaminases

In the placebo-controlled studies, for up to 24 weeks, events of increases in ALT and AST values (>3 × ULN) were reported in 3 patients (0.9%) and 2 patients (0.6%) treated with ritlecitinib 50 mg or higher, respectively. Most elevations were transient, and none led to discontinuation.

Paediatric population

A total of 181 adolescents (12 to <18 years of age) were enrolled in ritlecitinib alopecia areata studies.

The safety profile observed in adolescents was similar to that of the adult population.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Ritlecitinib was administered in placebo-controlled studies up to a single oral dose of 800 mg and multiple oral doses of 400 mg daily for 14 days. No specific toxicities were identified. In case of overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions (see «Undesirable effects»). There is no specific antidote for overdose with ritlecitinib. Treatment should be symptomatic and supportive.

Pharmacokinetics (PK) data up to and including a single oral dose of 800 mg in healthy adult volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 48 hours.

Properties/Effects

ATC-Code

L04AF08.

Mechanism of action

Ritlecitinib irreversibly and selectively inhibits Janus kinase (JAK) 3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family by blocking the adenosine triphosphate (ATP) binding site. In cellular settings, ritlecitinib specifically inhibits γ-common cytokines (IL-2, IL-4, IL-7, IL-15 and IL-21) signalling through JAK3-dependent common-γ chain receptors. Additionally, ritlecitinib inhibits TEC family of kinases, resulting in reduced cytolytic activity of NK cells and CD8+ T cells.

JAK3 and TEC family mediated signalling pathways are both involved in alopecia areata pathogenesis, although complete pathophysiology is still not understood.

Pharmacodynamics

Lymphocyte subsets

In patients with alopecia areata, treatment with ritlecitinib was associated with dose-dependent early decreases in absolute lymphocyte levels, T lymphocytes (CD3) and T lymphocyte subsets (CD4 and CD8). After the initial decrease, the levels partially recovered and remained stable up to 48 weeks. There was no change observed in B lymphocytes (CD19) in any treatment group. There was a dose dependent early decrease in NK cells (CD16/56) which remained stable at the lower level up to Week 48.

Immunoglobulins

In patients with alopecia areata, treatment with ritlecitinib was not associated with clinically meaningful changes in Immunoglobulin (Ig)G, IgM or IgA up to Week 48, indicating a lack of systemic humoral immunosuppression.

Cardiac electrophysiology

At 12 times the mean maximum exposure of the 50 mg once daily dose in patients with alopecia areata, there was no clinically relevant effect on the QTc interval.

Clinical efficacy

The efficacy and safety of ritlecitinib was evaluated in a pivotal, randomised, double-blind, placebo-controlled study (study AA-I) in alopecia areata patients 12 years of age and older with ≥50% scalp hair loss, including alopecia totalis and alopecia universalis. The dose-response of ritlecitinib was also evaluated in this study. The study treatment period consisted of a placebo-controlled 24-week period and a 24-week extension period. Study AA-I evaluated a total of 718 patients who were randomised to one of the following treatment regimens for 48 weeks: 1) 200 mg once daily for 4 weeks followed by 50 mg once daily for 44 weeks; 2) 200 mg once daily for 4 weeks followed by 30 mg once daily for 44 weeks; 3) 50 mg once daily for 48 weeks; 4) 30 mg once daily for 48 weeks; 5) 10 mg once daily for 48 weeks; 6) placebo for 24 weeks followed by 200 mg once daily for 4 weeks and 50 mg once daily for 20 weeks; or 7) placebo for 24 weeks followed by 50 mg for 24 weeks.

This study assessed as primary outcome the proportion of subjects who achieved a SALT (Severity of Alopecia Tool) score of ≤10 (90% or more scalp hair coverage) at Week 24. Additionally, this study assessed as key secondary outcome the Patient's Global Impression of Change (PGI-C) response at Week 24 and also assessed as secondary outcomes SALT score of ≤20 (80% or more scalp hair coverage) at Week 24 and improvements in regrowth of eyebrows and/or eyelashes at Week 24.

Baseline characteristics

Male or female patients 12 years of age and older, were assessed in study AA-I. All patients had alopecia areata with ≥50% scalp hair loss (SALT [Severity of Alopecia Tool] score ≥50) without evidence of terminal hair regrowth within the previous 6 months and with the current episode of scalp hair loss ≤10 years and no other known cause of hair loss (e.g., androgenetic alopecia).

Across all treatment groups 62.1% were female, 68.0% were White, 25.9% were Asian, and 3.8% were Black or African American. The mean age of patients was 33.7 years and the majority (85.4%) were adults (≥18 years of age). A total of 105 (14.6%) patients 12 to <18 years of age and 20 (2.8%) patients 65 years of age and older were enrolled. The mean (SD) baseline absolute SALT score ranged from 88.3 (16.87) to 93.0 (11.50) across treatment groups; among patients without alopecia totalis/alopecia universalis at baseline, the mean SALT score ranged from 78.3 to 87.0. The majority of patients had abnormal eyebrows (83.0%) and eyelashes (74.7%) at baseline across treatment groups. The median duration since alopecia areata diagnosis was 6.9 years and the median duration of the current alopecia areata episode was 2.5 years. Randomisation was stratified by alopecia totalis/alopecia universalis status with 46% of patients classified as alopecia totalis/alopecia universalis based upon a baseline SALT score of 100.

Clinical response

A significantly greater proportion of patients achieved SALT ≤10 response with ritlecitinib 50 mg compared to placebo at Week 24 (Table 2). The SALT ≤10 response rate for ritlecitinib 50 mg increased further at Week 48 (Figure 1).

A significantly greater proportion of patients achieved Patient's Global Impression of Change (PGI-C) response with ritlecitinib 50 mg compared to placebo at Week 24 (Table 2) with response rates continuing to increase through Week 48 (Figure 1).

A significantly greater proportion of patients achieved a SALT ≤ 20 response with ritlecitinib 50 mg compared to placebo at Week 24 (Table 2). The SALT ≤ 20 response rate increased further at Week 48.

Improvements in regrowth of eyebrows and/or eyelashes were seen at Week 24 (Table 2) with ritlecitinib 50 mg among patients with abnormal eyebrows and/or eyelashes at baseline with further increases seen at Week 48.

Treatment effects at Week 24 in subgroups (age, gender, race, region, weight, duration of disease since diagnosis, duration of current episode, prior pharmacologic treatment) were consistent with the results in the overall study population. Treatment effects at Week 24 in the alopecia totalis/alopecia

universalis subgroup were lower compared to the non-alopecia totalis/non-alopecia universalis subgroup. Treatment effects at Week 24 in adolescents 12 to less than 18 years of age were consistent with the results in the overall study population.

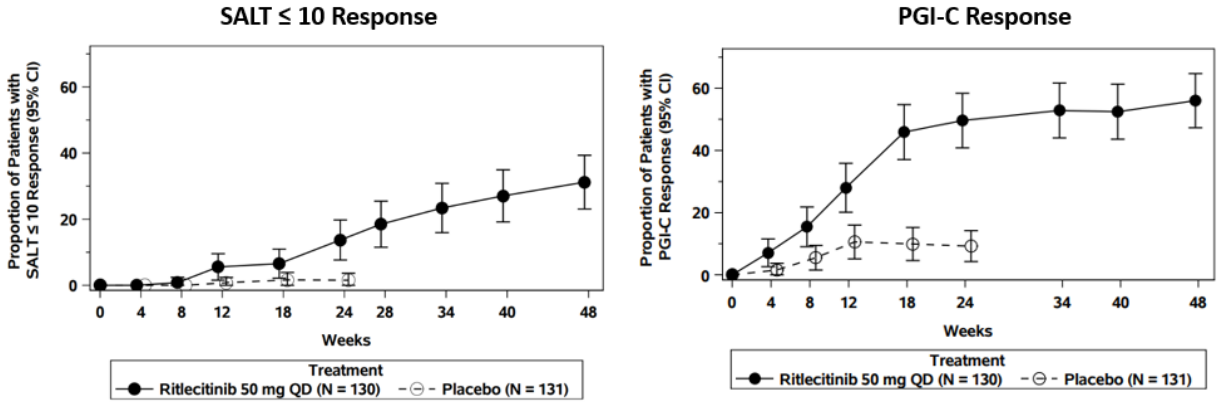
Table 2. Efficacy results of ritlecitinib at week 24

Endpoint	*Ritlecitinib 50 mg once daily (N = 130) % Responders*	*Placebo (N = 131) % Responders*	*Difference from placebo (95% CI)*
SALT ≤10 response[a,b]	13.4	1.5	11.9 (5.4, 18.3)
PGI-C response[b,c]	49.2	9.2	40.0 (28.9, 51.1)
SALT ≤20 response[d,e]	23.0	1.6	21.4 (13.4, 29.5)
EBA response[f]	29.0	4.7	24.3 (14.8, 34.5)
ELA response[g]	28.9	5.2	23.7 (13.6, 34.5)

Abbreviations: EBA = eyebrow assessment; ELA = eyelash assessment; CI = confidence interval; N = total number of patients; PGI-C = Patient's Global Impression of Change; SALT = Severity of Alopecia Tool

a. SALT ≤10 responders were patients with scalp hair loss of ≤10%. SALT scores range from 0 to 100 with 0 = no scalp hair loss and 100 = total scalp hair loss.
b. Statistically significant with adjustment for multiplicity.
c. PGI-C responders were patients with a score of «moderately improved» or «greatly improved» based upon a 7-point scale from «greatly improved» to «greatly worsened».
d. SALT ≤20 responders were patients with scalp hair loss of ≤20%. SALT scores range from 0 to 100 with 0 = no scalp hair loss and 100 = total scalp hair loss.
e. Statistically significant.
f. EBA response is defined as at least a 2-grade improvement from baseline or normal EBA score on a 4-point scale in patients with abnormal eyebrows at baseline.
g. ELA response is defined as at least a 2-grade improvement from baseline or normal ELA score on a 4-point scale in patients with abnormal eyelashes at baseline.

Figure 1. SALT ≤10 and PGI-C response through Week 48



Abbreviations: CI=confidence interval; N=total number of patients; PGI-C=Patient Global Impression of Change; QD=once daily; SALT=Severity of Alopecia Tool

Pharmacokinetics

Absorption

The absolute oral bioavailability of ritlecitinib is about 64%. Based on oral and intravenous administration of the labelled active substance, the relative urinary recovery (oral/intravenous) of labelled compounds was about 89%, indicating a high fraction absorbed (f_a). Peak plasma concentrations are reached within 1 hour following multiple oral doses. Food does not have a clinically significant impact on the extent of ritlecitinib absorption, as a high-fat meal decreased the ritlecitinib C_{max} by ~32% and increased AUC_{inf} by ~11%. In placebo-controlled studies, ritlecitinib was administered without regard to meals (see «Dosage/Administration»).

Distribution

After intravenous administration, the volume of distribution of ritlecitinib is about 74 l. Approximately 14% of circulating ritlecitinib is bound to plasma proteins, primarily albumin. The blood/plasma distribution ratio of ritlecitinib is 1.62.

Metabolism

The metabolism of ritlecitinib is mediated by multiple isoforms of Glutathione S-transferase (GST: cytosolic GST A1/3, M1/3/5, P1, S1, T2, Z1, and microsomal Membrane Associated Proteins involved in Eicosanoid and Glutathione metabolism [MAPEG]1/2/3) and CYP enzymes (CYP3A, CYP2C8, CYP1A2, and CYP2C9), with no single clearance route contributing more than 25%.

In a human radiolabeled study, ritlecitinib was the most prevalent circulating species (30.4% of circulating radioactivity) after oral administration, with a major cysteine conjugate metabolite M2 (16.5%), which is pharmacologically inactive.

Elimination

Ritlecitinib is eliminated primarily by metabolic clearance mechanisms, with approximately 4% of the dose excreted as unchanged active substance in urine. Approximately 66% of radiolabeled ritlecitinib dose is excreted in the urine and 20% in the faeces. Following multiple oral doses, steady state was reached approximately by Day 4 due to non-stationary PK. The steady state PK parameters of AUC_{tau} and C_{max} appeared to increase in an approximately dose-proportional manner up to 200 mg with the mean terminal half-life ranging from 1.3 to 2.3 hours.

Kinetics in specific patient groups

Body weight, gender, genotype, race and age

Body weight, gender, GST P1, M1, and T1 genotype, race and age did not have a clinically meaningful effect on ritlecitinib exposure.

Adolescents (≥12 to <18 years)

Based on population PK analysis, there was no clinically relevant difference in ritlecitinib exposures in adolescent patients compared to adults.

Paediatric (<12 years)

The PK of ritlecitinib in children under 12 years of age have not yet been established.

Renal impairment

The AUC_{24} and C_{max} in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min) was about 55% and 44% higher, respectively, compared with matched participants with normal renal functions. This was confirmed by popPK analysis. These differences are not considered clinically significant. Ritlecitinib was not studied in patients with mild (eGFR 60 to <90 mL/min) or moderate (eGFR 30 to <60 mL/min) renal impairment. The eGFR and classification of renal function status of participants was done using the Modification of Diet in Renal Disease (MDRD) formula.

Hepatic impairment

Patients with moderate (Child Pugh B) hepatic impairment had an 18.5% increase in ritlecitinib AUC_{24} compared to participants with normal hepatic function. Ritlecitinib was not studied in patients with mild (Child Pugh A) hepatic impairment. However, based on the results obtained in patients with moderate hepatic impairment, a clinically significant increase in ritlecitinib exposure is not expected in these patients. Ritlecitinib has not been studied in patients with severe (Child Pugh C) hepatic impairment (see «Contraindications»).

Preclinical data

General toxicity

Decreased lymphocyte counts and decreased lymphoid cellularity of organs and tissues of the immune and haematolymphopoietic systems were observed in nonclinical toxicity studies and were attributed to the pharmacological properties (JAK3/TEC inhibition) of ritlecitinib.

Chronic administration of ritlecitinib to Beagle dogs led to the occurrence of axonal dystrophy at systemic exposures of at least 7.4-times the expected exposure in patients treated with 50 mg per day (based on unbound AUC24). Axonal dystrophy is presumably related to binding to off-target neuronal proteins. It is not known if axonal dystrophy occurred in dogs at lower systemic exposures. At a systemic exposure that was 33-times above the expected exposure in patients treated with 50 mg per day (based on unbound AUC24), axonal dystrophy was associated with neurological hearing loss. While these findings proved to reverse after dosing cessation of ritlecitinib in dogs, a risk to patients at a chronic dosing regimen cannot be fully excluded.

Genotoxicity

Ritlecitinib was not mutagenic in the bacterial mutagenicity assay (Ames assay). Ritlecitinib is not aneugenic or clastogenic at exposures equal to 130 times the MRHD on an unbound AUC basis based on the results of the *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumorigenicity was observed in the 6-month Tg.ras H2 mice administered ritlecitinib at exposures equal to 11 times the MRHD on an unbound AUC basis. In a 2-year rat carcinogenicity study, a higher incidence of benign thymomas in female rats and benign thyroid follicular adenomas in male rats was noted following ritlecitinib administration at exposures equal to 29 times the MRHD on

an unbound AUC basis. At this ritlecitinib exposure, a higher incidence of malignant thymomas in female rats cannot be excluded. No ritlecitinib-related thymomas or thyroid follicular adenomas were observed at exposures equal to 6.3 times the MRHD on an unbound AUC basis.

Reproductive and developmental toxicity

Ritlecitinib had no effects on female rat fertility at exposures equal to 55 times the MRHD on an unbound AUC basis. Effects on male rat fertility were noted (higher preimplantation loss resulting in lower number of implantation sites and corresponding lower litter size in naïve females mated with ritlecitinib dosed males) at exposure equal to 55 times the MRHD on an unbound AUC basis. No effects on male fertility were noted at exposures equal to 14 times the MRHD on an unbound AUC basis. No effects on spermatogenesis (sperm counts, sperm production rate, motility, and morphology) were noted at any dose in the rat fertility study.

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.

In a juvenile rat toxicity study, oral administration of ritlecitinib from postnatal day 10 to 60 (comparable to infant through adolescence human age) was not associated with effects on the nervous or skeletal systems.

Lactation

Following administration of ritlecitinib to lactating rats, concentrations of ritlecitinib in milk over time were higher than those in plasma, where the mean milk to plasma AUC ratio was determined to be 2.2.

Other information

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the container.

Special precautions for storage

Do not store above 30 °C.

Store in the original package to protect the content from light.

Keep out of reach of children.

Zulassungsnummer

69695 (Swissmedic).

Packungen

Litfulo 50 mg hard capsules: 30 (blister packaging). [B]

Zulassungsinhaberin

Pfizer AG, Zürich.

Stand der Information

October 2024.

LPD V003