PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**LITFULO**™

Ritlecitinib Capsules

Capsule, 50 mg ritlecitinib (as ritlecitinib tosylate), Oral use

Selective JAK3 & TEC Family Kinase Inhibitor

Pfizer Canada ULC
17,300 TransCanada Highway
Kirkland, Quebec, H9J 2M5

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RECENT MAJOR LABEL CHANGES

Not applicable	Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LITFULO (ritlecitinib) is indicated for:

- the treatment of adults and adolescents 12 years and older with severe alopecia areata.

Limitations of Use: Not recommended for use in combination with JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

1.1 Pediatrics

12-17 years of age: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LITFULO in pediatric patients 12-17 years of age has been established for severe alopecia areata.

Under 12 years of age: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients under 12 years of age.

1.2 Geriatrics

There are limited data in patients ≥ 65 years of age. As there is a higher incidence of infections in the geriatric population in general, caution should be used when treating geriatric patients [see 4.2 Recommended Dose and Dosage Adjustment; 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

- LITFULO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- LITFULO is contraindicated in pregnant and lactating/breastfeeding women [see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding].
- LITFULO is contraindicated in severe hepatic impairment [see 10.3 Pharmacokinetics, Special Populations and Conditions].

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Serious Infections

Patients treated with LITFULO may be at increased risk for developing serious infections that may lead to hospitalization or death [see 7 WARNINGS AND PRECAUTIONS; 8 ADVERSE REACTIONS].

Reported infections from Janus kinase (JAK) inhibitors used to treat inflammatory conditions:

- Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test for latent TB before and during therapy; start treatment of latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

Treatment with LITFULO should be avoided in patients with an active, serious infection. If a serious or opportunistic infection develops during treatment, interrupt LITFULO until the infection is controlled. The risks and benefits of treatment with LITFULO should be carefully considered prior to initiating therapy in patients with chronic or recurrent infections.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with LITFULO [see 7 WARNINGS AND PRECAUTIONS].

Malignancies
Malignancies were reported in patients treated with LITFULO [see 7 WARNINGS AND PRECAUTIONS].

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of alopecia areata. 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 of treatment.

Recommended Evaluations and Immunizations Prior to Treatment Initiation

Perform the following evaluations prior to LITFULO initiation:

- Patients should be screened for tuberculosis (TB) before starting therapy. LITFULO should not be given to patients with active TB. Anti-TB therapy should be started prior to initiating therapy with LITFULO in patients with a new diagnosis of latent TB or previously untreated latent TB. In patients with a negative latent TB test, consider anti-TB therapy before initiating treatment with LITFULO in those at high risk [see 7 WARNINGS AND PRECAUTIONS].
- Viral hepatitis screening in accordance with clinical guidelines: LITFULO initiation is not recommended in patients with hepatitis B or hepatitis C [see 7 WARNINGS AND PRECAUTIONS].
- Treatment with LITFULO should not be initiated in patients with an absolute lymphocyte count (ALC) <500/mm^3 or a platelet count <100,000/mm^3 [see 7 WARNINGS AND PRECAUTIONS].
- Blood work for liver enzymes should be drawn at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed and drug-induced liver injury is suspected, interrupt LITFULO [see 8 ADVERSE REACTIONS].
- Update immunizations according to current immunization guidelines [see 7 WARNINGS AND PRECAUTIONS].
- Skin examination for malignancy is recommended before treatment initiation and periodically thereafter, especially for patients who are at increased risk for skin cancer [see 7 WARNINGS AND PRECAUTIONS].

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage of LITFULO is 50 mg orally once daily.

Geriatric population

No dose adjustment is required for patients ≥65 years of age [see 10.3 Pharmacokinetics, Special Populations and Conditions].

Pediatric population

No dose adjustment is required for patients 12 to <18 years of age [see 10.3 Pharmacokinetics, Special Populations and Conditions].

Under 12 years of age: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Hepatic Impairment

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment [see 10.3 Pharmacokinetics, Special Populations and Conditions]. LITFULO is contraindicated in patients with severe hepatic impairment (Child Pugh C) [see 2 CONTRAINDICATIONS].

Renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment [see 10.3 Pharmacokinetics, Special Populations and Conditions].

LITFULO 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.

Treatment Interruption or Discontinuation

There is variability in time to response to treatment. Consideration should be given to discontinuing patients who show no evidence of therapeutic benefit after 36 weeks of treatment. The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis.

If treatment interruption is indicated, a temporary treatment interruption for less than 6 weeks is not expected to result in significant loss of regrown scalp hair.

Infections

If a patient develops serious infection or an opportunistic infection, LITFULO should be interrupted until the infection is controlled [see 7 WARNINGS AND PRECAUTIONS].

Hematologic abnormalities

Recommendations for LITFULO treatment interruption or discontinuation for hematologic abnormalities are summarized in Table 1.

Monitoring during Treatment

Consider screening patients at high risk for TB during treatment with LITFULO.

Table 1: Laboratory Measures and Monitoring Guidance

Laboratory Measure	Monitoring guidance	Recommendation
Platelet Count	Before treatment initiation and 4 weeks after initiation, and thereafter according to routine patient management. [see 7 WARNINGS AND PRECAUTIONS]	Treatment should be discontinued if platelet count is <50,000/mm^3
Lymphocytes		Treatment should be interrupted if ALC is <500/mm^3 and may be restarted once ALC returns above this value.

ALC = absolute lymphocyte count

Effects of LITFULO on CYP3A Substrates

Caution should be exercised with concomitant use of LITFULO with CYP3A substrates where small concentration changes may lead to serious adverse reactions, and dose adjustment recommendations for the CYP3A substrate in accordance with approved product labeling should be considered [see 10.3 Pharmacokinetics].

Effects of LITFULO on CYP1A2 Substrates

Caution should be exercised with concomitant use of LITFULO with CYP1A2 substrates where small concentration changes may lead to serious adverse reactions, and dose adjustment recommendations for the CYP1A2 substrate in accordance with approved product labeling should be considered [see 10.3 Pharmacokinetics].

4.4 Administration

LITFULO is to be taken orally once daily with or without food [see 10.3 Pharmacokinetics**]**. Capsules should be swallowed whole and should not be crushed, split, or chewed.

4.5 Missed Dose

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.

5 OVERDOSAGE

There is no specific antidote for overdose with LITFULO. Treatment should be symptomatic and supportive, and patients should be monitored for signs and symptoms of adverse reactions [see 8 ADVERSE REACTIONS].

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Route of Administration, Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral use	Capsule / 50 mg /	Crospovidone, FD&C BLUE NO. 1, ferric oxide yellow, glyceryl dibehenate, hypromellose,

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
	ritlecitinib (80.128 mg ritlecitinib tosylate)	lactose monohydrate, microcrystalline cellulose, titanium dioxide

The 50 mg capsule is opaque with a yellow body and blue cap. The body is printed with “RCB 50” and the cap is printed with “Pfizer” in black.

Packaging

LITFULO is packaged in blister or bottle. Each blister pack contains 30 capsules (10 capsules x 3 blister cards), and each bottle contains 28 capsules.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Malignancy (including non melanoma skin cancer)

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

It is not known whether selective JAK3 inhibition may be associated with adverse reactions of Janus Kinase (JAK) inhibition predominantly involving JAK1 and JAK2. In a large randomised active controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis (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.

Limited clinical data are available to assess the potential relationship of exposure to ritlecitinib and the development of malignancies. Long-term safety evaluations are ongoing. Patients should be informed that LITFULO may increase their risk of certain cancers, including skin cancers and be instructed to notify their healthcare professional if they have ever had any type of cancer. 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 for skin cancer.

Cardiovascular

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.

It is not known whether selective JAK3 inhibition may be associated with adverse reactions of JAK inhibition predominantly involving JAK1 and JAK2. 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 higher rate of venous thromboembolism including DVT and PE were observed with tofacitinib compared to TNF inhibitors.

Long-term safety evaluations for ritlecitinib are ongoing. 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 reevaluation is recommended. The risks and benefits of ritlecitinib treatment should be considered prior to initiating therapy in patients.

Driving and Operating Machinery

LITFULO has no known influence on the ability to drive and use machines.

Hematologic

Treatment with LITFULO was associated with decreases in lymphocytes and platelets [see 8 ADVERSE REACTIONS]. Prior to initiating treatment with LITFULO, ALC and platelet counts should be performed. Treatment with LITFULO should not be initiated in patients with an ALC <500/mm^3 or with a platelet count <100,000/mm^3. ALC and platelet counts are recommended to be performed 4 weeks after initiation of therapy with ritlecitinib, and thereafter according to routine patient management. After initiating treatment with LITFULO, treatment interruption or discontinuation are recommended based on ALC and platelet count abnormalities [see 4.2 Recommended Dose and Dosage Adjustment].

Infections

Serious Infections

Serious infections have been reported in patients receiving LITFULO. The most frequent serious infections have been appendicitis, COVID-19 infection (including pneumonia), and sepsis [see 8 ADVERSE REACTIONS]. Among opportunistic infections, multi-dermatomal herpes zoster was reported with LITFULO. Treatment with LITFULO should be avoided in patients with an active, serious infection.

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

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of serious infection or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis 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 LITFULO. Treatment should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with LITFULO 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. Prescribers should evaluate whether interrupting treatment with LITFULO for alopecia areata is the best course of action for an individual patient. If interrupted, LITFULO may be resumed once the infection is controlled.

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

Tuberculosis

Patients should be screened for tuberculosis (TB) before starting therapy. LITFULO should not be given to patients with active TB. Anti-TB therapy should be started prior to initiating therapy with LITFULO in patients with a new diagnosis of latent TB or previously untreated latent TB. In patients with a negative latent TB test, consider anti-TB therapy before initiating treatment with LITFULO in those at high risk and consider screening patients at high risk for TB during treatment with LITFULO.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was reported in clinical studies [see 8 ADVERSE REACTIONS]. If a patient develops herpes zoster, consider interrupting treatment until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with LITFULO. Patients with evidence of hepatitis B or C infection were excluded from clinical studies. 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.

Immune

Atopic dermatitis

Flares of atopic dermatitis were seen in clinical trials with LITFULO. Healthcare professionals should monitor for relevant symptoms.

Hypersensitivity

Reactions such as urticaria, rash, and anaphylactic reaction that may reflect drug hypersensitivity, including serious reactions, have been observed in patients receiving LITFULO in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue LITFULO and institute appropriate therapy [see 8 ADVERSE REACTIONS].

Vaccinations

No data are available on the response to vaccination in patients receiving LITFULO. Use of live attenuated vaccines should be avoided during or shortly prior to initiating treatment. Prior to initiating LITFULO, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

Monitoring and Laboratory Tests

Recommendations for LITFULO treatment interruption or discontinuation for hematologic abnormalities are summarized in Table 1.

Neurologic

Ritlecitinib-related axonal dystrophy has been observed in chronic beagle dog toxicity studies [see 16 NON-CLINICAL TOXICOLOGY]. Treatment with ritlecitinib should be discontinued if unexplained neurological symptoms occur.

Reproductive Health: Female and Male Potential

Persons of childbearing potential should be advised to use effective contraception during treatment and for 1 month following the final dose of LITFULO. Consider pregnancy planning and prevention for persons of childbearing potential. Patients should be instructed to discontinue LITFULO if they become pregnant as the use of LITFULO is contraindicated in pregnancy [see 2 CONTRAINDICATIONS].

- **Fertility**

There were no effects on male or female rat fertility at clinically relevant exposures [see 16 NON-CLINICAL TOXICOLOGY].

7.1 Special Populations

7.1.1 Pregnant Women

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 [see 16 NON-CLINICAL TOXICOLOGY]. LITFULO must not be used during pregnancy [see 2 CONTRAINDICATIONS].

7.1.2 Breast-feeding

There are no data on the presence of ritlecitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Ritlecitinib was excreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and LITFULO must not be used during breastfeeding [see 2 CONTRAINDICATIONS].

7.1.3 Pediatrics

A total of 181 pediatric patients ages 12 to <18 years were enrolled in alopecia areata clinical trials, with 105 pediatric patients ages 12 to <18 years with alopecia areata randomized in a pivotal, double-blind, placebo-controlled trial (Trial AA-I). The safety profile in the adolescent population was generally similar to adults.

LITFULO has not been investigated in pediatric patients under 12 years of age. Therefore, Health Canada has not authorized an indication for pediatric use in patients under 12 years of age.

7.1.4 Geriatrics

≥65 years of age: A total of 28 patients enrolled in alopecia areata studies were 65 years of age and older, and none were 75 years of age and older. Clinical trials of LITFULO did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

As there is a higher incidence of infections in the geriatric-population in general, caution should be used when treating geriatric patients. Age appeared to be a risk factor for lower ALC in patients ≥ 65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse drug reactions (ADRs) occurring in ≥2% of patients treated with LITFULO in placebo-controlled studies were diarrhea (9.2%), acne (6.2%), upper respiratory tract infections (6.2%), urticaria (4.6%), rash (3.8%), folliculitis (3.1%) and dizziness (2.3%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of LITFULO was evaluated in three randomized, placebo-controlled clinical trials and one long-term trial in patients with alopecia areata, including alopecia totalis and alopecia universalis, who were 12 years of age and older. A total of 1628 patients were treated with ritlecitinib, representing 2085 patient-years of exposure. There were 1011 patients with at least 1 year of exposure to ritlecitinib. In the placebo-controlled period of clinical trials in alopecia areata, a total of 668 patients were exposed to ritlecitinib, with 130 receiving 50 mg once daily for up to 24 weeks. The median age of patients was 33 years, 105 (11.9%) patients were 12 to <18 years old and 22 (2.5%) patients were 65 years of age or older. The majority of patients were White (70.7%) and female (63.6%).

Dose-related adverse drugs reactions (ADRs) from these studies are presented by Preferred Term (PT) in Table 3.

Table 3: Adverse Reactions Reported in ≥1% of Patients in Clinical Trials of LITFULO for the Treatment of Alopecia Areata[a] up to 24 weeks

	LITFULO 50 mg N=130 n (%)	**Placebo N=213 n (%)**
Gastrointestinal disorders		
Diarrhea	12 (9.2)	8 (3.8)
Infections and infestations		
Upper respiratory tract infection	8 (6.2)	16 (7.5)
Folliculitis	4 (3.1)	4 (1.9)
Herpes zoster	2 (1.5)	0
Investigations		
Blood creatine phosphokinase increased	2 (1.5)	0
Nervous system disorders		
Dizziness	3 (2.3)	3 (1.4)
Skin and subcutaneous tissue disorders		
Acne	8 (6.2)	10 (4.7)
Urticaria	6 (4.6)	3 (1.4)
Rash	5 (3.8)	2 (0.9)

a. reported in ≥1% of patients and at a higher rate than placebo for up to 24 weeks except URTI

Specific Adverse Reactions

Exposure adjusted incidence rates were adjusted by clinical trial size for all adverse reactions reported in this section.

Overall Infections

In the placebo-controlled trials, for up to 24 weeks, overall infections were reported in 66 patients (80.35 per 100 patient-years) treated with placebo and 43 patients (74.53 per 100 patient-years) treated with LITFULO 50 mg. In all 5 clinical trials, including the long-term trial, overall infections were reported in 645 patients (50.71 per 100 patient-years) treated with LITFULO 50 mg or higher.

Serious Infections

In the placebo-controlled trials, for up to 24 weeks, no serious infections were reported in patients treated with placebo or LITFULO 50 mg. In the ritlecitinib 200/50 mg group (200 mg once daily for 4 weeks followed by 50 mg once daily), 2 patients (2.66 per 100 patient-years) reported serious infections. In all 5 clinical trials, serious infection was reported in 12 patients (0.66 per 100 patient-years) treated with LITFULO 50 mg or higher. The most common serious infections were appendicitis, COVID-19 infection (including pneumonia), and sepsis.

Herpes Zoster

In the placebo-controlled trials, for up to 24 weeks, herpes zoster was reported in 2 patients (2.74 per 100 patient-years) treated with LITFULO 50 mg and 0 patients treated with placebo. In all 5 clinical trials, including the long-term trial, herpes zoster was reported in 21 patients (1.17 per 100 patient years) treated with LITFULO 50 mg or higher. Opportunistic infections of multi-dermatomal herpes zoster were reported in 1 patient (0.50 per 100 patient-years) treated with 200/50 mg ritlecitinib in the placebo-controlled trials and 2 patients (0.1 per 100 patient-years) treated with LITFULO 50 mg or higher in all clinical trials.

Elevated Liver Enzymes

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 LITFULO 50 mg or higher, respectively. Most elevations were transient, and none led to discontinuation.

Urticaria

In the placebo-controlled trials, for up to 24 weeks, urticaria was reported in 28 treated patients in all ritlecitinib doses studied and 3 patients treated with placebo. The rate of urticaria was 8.23 per 100 patient-years in patients treated with ritlecitinib 50 mg and 4.03 per 100 patient-years in patients treated with placebo. Across clinical trials, including the long-term trial, urticaria was reported in 76 patients treated with LITFULO 50 mg or higher. Among all patients treated with ritlecitinib 50 mg or higher in the integrated safety analysis, the rate of urticaria was 4.10 per 100 patient-years. The median time to onset of an initial event was 8 weeks; median duration of urticaria was 7 days. Most of the cases were mild to moderate in severity.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

A total of 181 pediatric patients ages 12 to <18 years were enrolled in alopecia areata clinical trials, with 105 pediatric patients ages 12 to <18 years with alopecia areata randomized in a pivotal, double-blind, placebo-controlled trial (Trial AA-I). The adverse reaction profile in these adolescent patients was generally similar to adults. The frequency of acne and upper respiratory tract infections (URTIs) was higher in pediatric patients than in adults.

8.3 Less Common Clinical Trial Adverse Reactions

Immune system disorders: Hypersensitivity, anaphylactic reaction

Investigations: Platelet count decreased, lymphocyte count decreased

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Creatinine Phosphokinase Elevations (CPK)

In the placebo-controlled trials, for up to 24 weeks, events of blood CPK increased were reported in 5 (2.5%) patients treated with LITFULO 50 mg and 2 (0.7%) patients treated with placebo. 2 (0.4%) patients treated with LITFULO 50 mg or higher and 1 (0.4%) patient treated with placebo were discontinued due to AEs of blood CPK increased. In all 5 clinical trials, including the long-term trial, events of blood CPK increased were reported in 46 (3.0%) patients treated with LITFULO 50 mg or higher. 4 (0.3%) patients were discontinued due to AEs of blood CPK increased. There were no reports of myopathy or rhabdomyolysis.

Decreased Lymphocyte Counts

In all 5 clinical trials, including the long-term trial, confirmed ALC <500/mm^3 occurred in 1 patient (<0.1%) treated with LITFULO 50 mg. Age appeared to be a risk factor for lower ALC in patients ≥65 years of age.

Decreased Platelet Count

In the placebo-controlled trials, for up to 24 weeks, treatment with LITFULO 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. In all 5 clinical trials, including the long-term trial, 1 patient (<0.1%) had a confirmed platelet count <100,000/mm^3. No patient had a confirmed platelet count <75,000/mm^3.

8.5 Post-Market Adverse Reactions

Not applicable

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

CYP3A inducers decrease plasma concentrations of LITFULO, and LITFULO increases the plasma concentration of CYP3A substrates and CYP1A2 substrates.

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

The drugs listed in table 4 and table 5 are based on drug interaction studies.

Effect of Co-administered Drugs on Pharmacokinetics of Ritlecitinib

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%. Hence, drugs 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 [see 10.3 Pharmacokinetics].

Table 4: Established or Potential Drug-Drug Interactions – Effect of Co-administered Drugs on Pharmacokinetics of Ritlecitinib

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
Rifampin	CT	Co-administration of multiple 600 mg doses of rifampin (a potent inducer of CYP3A4, CYP2C19, CYP2C9 and CYP2B6) decreased AUC of ritlecitinib at 50 mg by approximately ~44% and C_{max} by ~25%.	Coadministration with strong CYP3A inducers is not recommended.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Effect of Ritlecitinib on Pharmacokinetics of Co-administered Drugs

Table 5: Established or Potential Drug-Drug Interactions – Effect of Ritlecitinib on Pharmacokinetics of Co-administered Drugs

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
Caffeine	CT	Multiple doses of 200 mg once daily ritlecitinib increased the AUC and C_{max} of caffeine, a substrate for CYP1A2 at 100 mg by approximately 265% and 109%, respectively.	Caution should be exercised with concomitant use of LITFULO with CYP1A2 substrates where small concentration changes may lead to serious adverse reactions, and dose adjustment recommendations for the CYP3A substrate should be considered.
Midazolam	CT	Ritlecitinib at doses of 200 mg QD increased the midazolam (a CYP3A4 and CYP3A5 substrate)	Caution should be exercised with concomitant use of LITFULO with CYP3A

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
		AUC and C_{max} ~2.7- and 1.8-fold, respectively.	substrates where small concentration changes may lead to serious adverse reactions, and dose adjustment recommendations for the CYP3A substrate should be considered.
Sumatriptan	CT	Single 400 mg dose of ritlecitinib increased sumatriptan (a substrate of OCT1) at 25 mg, AUC 130% and C_{max} 87%.	Caution should be exercised with concomitant use of ritlecitinib with OCT1 substrates where small concentration changes may lead to serious adverse reactions.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

LITFULO may be administered regardless of food intake.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been evaluated.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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). For the 50 mg QD dose, there was an initial decrease in median lymphocyte levels which remained consistent up to Week 48. There was no change observed in B lymphocyte (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 IgG, 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.

10.3 Pharmacokinetics

Table 6: Summary of Ritlecitinib Non-compartmental Pharmacokinetics in Healthy Participants and Alopecia Areata (AA) Patients

	Ritlecitinib 50 mg QD at Steady-state[a]	
	Healthy Partipants	**AA Participants**
C_{max} (ng/mL)	315.2 (38)	397.6 (44)
AUC_t (ng•hr/mL)	540.1 (38)	1411 (47)

a. Geometric Mean (Geometric %CV) for all

Abbreviations: C_{max} = Maximum plasma concentration; ng = nanogram; mL = milliliter; hr = hour(s); AUC_t = Area under the concentration-time profile from time zero to time tau (τ), the dosing interval, where tau = 24 hours for QD dosing and 12 hours for BID dosing; QD = once daily

Absorption

Ritlecitinib is well absorbed to the extent of ~89% (f_a) after the oral administration with the absolute oral bioavailability of ~64%. Peak plasma concentrations are reached within 1 hour. Steady state can be reached approximately by Day 4.

Effect of food

Administration of the 100 mg ritlecitinib tosylate capsule with a high-fat, high-calorie meal delayed absorption by 2 hours (median T_{max} of 3 hours), decreased the C_{max} by 32%, and increased AUC_{inf} by 11%. LITFULO was administered without regard to meals in clinical studies and may be taken without regard to food.

Distribution:

After intravenous administration, the volume of distribution of ritlecitinib is about 74 L. Approximately 14% of circulating ritlecitinib is bound to plasma proteins. 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 intravenous 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 drug in urine. The metabolites of ritlecitinib are excreted in urine (66% of recovered radioactivity) and feces (20%). 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 with the mean terminal half-life ranging from 1.3 to 2.3 hours.

Special Populations and Conditions

- **Pediatrics**

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.

Pediatric (<12 years)

The pharmacokinetics of ritlecitinib in pediatric patients under 12 years of age have not been established.

- **Geriatrics**

PopPK analysis including 65-74 years old group did not identify age as a clinically meaningful factor on ritlecitinib exposure.

- **Sex**

Sex did not have a clinically meaningful effect on ritlecitinib exposure.

- **Pregnancy and Breastfeeding**

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 [see 16 NON-CLINICAL TOXICOLOGY]. LITFULO is contraindicated during pregnancy.

There are no data on the presence of ritlecitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Ritlecitinib was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and LITFULO is contraindicated during pregnancy and breastfeeding [see 2 CONTRAINDICATIONS].

- **Genetic Polymorphism**

GST P1, M1 and T1 genotype did not have a clinically meaningful effect on ritlecitinib exposure.

- **Ethnic Origin**

Ethnic origin did not have a clinically meaningful effect on ritlecitinib exposure.

- **Hepatic Insufficiency**

Patients with moderate (Child Pugh B) hepatic impairment had an 18.5% increase in ritlecitinib AUC_{24} compared to participants with normal hepatic function. Based on the above considerations, no dose

adjustment is required in patients with mild or moderate hepatic impairment [see 4.2 Recommended Dose and Dosage Adjustment]. In clinical studies, ritlecitinib has not been studied in patients with severe (Child Pugh C) hepatic impairment and is contraindicated for use in these patients [see 2 CONTRAINDICATIONS]

- **Renal Insufficiency**

The AUC_{24} observed in patients with severe renal impairment (eGFR <30 mL/min) was 55.2% higher compared with the AUC_{24} in matched participants with normal renal functions. Ritlecitinib has not been studied in patients with mild (eGFR 60 to <90 mL/min) or moderate (eGFR 30 to <60 mL/min) renal impairment, as a clinically relevant increase in ritlecitinib exposure is not expected in these patients. The eGFR and classification of renal function status of patients was done using the Modification of Diet in Renal Disease (MDRD) formula. Ritlecitinib has not been studied in patients with ESRD or in renal transplant recipients.

- **Body Weight**

Body weight did not have a clinically meaningful effect on ritlecitinib exposure.

- **Age**

Age did not have a clinically meaningful effect on ritlecitinib exposure.

11 STORAGE, STABILITY AND DISPOSAL

Store LITFULO at room temperature (15°C to 30°C). Keep in original package.

Any unused LITFULO should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

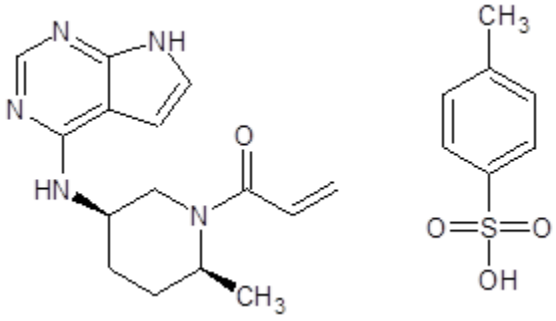
Drug Substance

Proper/Common name: ritlecitinib tosylate

Chemical name: 1-{(2*S*,5*R*)-2-Methyl-5-[(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}prop-2-en-1-one 4-methylbenzene-1-sulfonic acid

Molecular formula and molecular mass: $C_{22}H_{27}N_5O_4S$ and 457.55 Daltons (Da.)

Structural formula:



Physicochemical properties:

LITFULO (ritlecitinib) capsules are formulated with ritlecitinib tosylate (a salt of ritlecitinib).

Ritlecitinib tosylate is a white to off white to pale pink solid which is freely soluble in water.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy and safety of ritlecitinib was evaluated in a pivotal, randomized, double-blind, placebo-controlled study Study AA-I (B7981015) in alopecia areata patients 12 years of age and older with ≥50% scalp hair loss, including Alopecia Totalis (AT) and Alopecia Universalis (AU). 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 randomized for a total of 7 treatment sequences in a 2:2:2:2:1:1:1 manner to blinded ritlecitinib and matching placebo 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. Patients who completed the pivotal study were eligible to enroll in an open-label long-term study AA-II (B7981032).

Table 7: Summary of patient demographics for clinical trial in alopecia areata

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n
AA-I B7981015	A Phase 2b/3 Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Investigate the Efficacy and Safety of Ritlecitinib in Adult and Adolescent Alopecia Areata (AA) Participants With 50% or Greater Scalp Hair Loss	<u>Groups Treated with ritlecitinib:</u> A: 200 mg/50 mg once daily (QD) B: 200 mg/30 mg QD C: 50 mg/50 mg QD D: 30 mg/30 mg QD E: 10 mg/10 mg QD F: Placebo for 24 weeks followed by 200 mg/50 mg QD G: Placebo for 24 weeks followed by 50 mg QD	Total = 718 132 130 130 132 63 65 66	Mean 33.7 Min, Max (12, 73) years Adults: 613 Adolescents: 105	Male: 272 Female: 446

Abbreviation: QD = once daily

The recommended dose of ritlecitinib is 50 mg once daily and the results for this dose are discussed below.

Across all treatment groups 62.1% of patients were female, 68.0% were White, 25.9% were Asian, and 3.8% were Black or African American. The majority of patients (85.4%) were adults (≥18 years of age) with a mean age of 33.7 years. 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 baseline Severity of Alopecia Tool (SALT) score ranged from 88.3 to 93.0 across treatment groups; among patients without AT/AU 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. Randomization was stratified by AT/AU status with 46% of patients classified as AT/AU based upon a baseline SALT score of 100.

14.2 Study Results

This study assessed as primary outcome the proportion of patients who achieved a SALT (Severity of Alopecia Tool) score of ≤20 (80% or more scalp hair coverage) at Week 24. Additionally, this study assessed as secondary outcomes, SALT score of ≤10 (90% or more scalp hair coverage) at Week 24, change from baseline in SALT scores over time, and improvements in regrowth of eyebrows and/or eyelashes at Week 24. Patient's Global Impression of Change (PGI-C) response is a patient-reported outcome measure that asks the patient if there has been a global improvement or worsening in their disease status compared to the start of the study. PGI-C response (defined as a score of "moderately improved" or "greatly improved" based upon a 7 –point Likert scale from "greatly improved" to "greatly worsened) at Week 24 was assessed to evaluate treatment benefit from the patient's perspective and demonstrate value.

Assessment of scalp hair loss was based on the Severity of Alopecia Tool (SALT) score. At Week 24, a significantly greater proportion of patients had a SALT ≤20 response (20% or less of scalp hair loss) with LITFULO 50 mg compared to placebo (Table 8). The SALT ≤20 response rate for LITFULO increased further after Week 24 through Week 48. The percentage of patients achieving SALT ≤20 response by visit is shown in Figure 1. Statistical separation from placebo in SALT ≤20 response first occurred at Week 18 for LITFULO.

A significantly greater proportion of patients had a SALT ≤10 response (10% or less of scalp hair loss) with LITFULO 50 mg compared to placebo at Week 24 (Table 8). The SALT ≤10 response rate increased further at Week 48.

Significant improvement in the Patient's Global Impression of Change (PGI-C) for LITFULO 50 mg compared to placebo was seen at Week 24 with response rates continuing to increase through Week 48 (Figure 2).

Patients receiving LITFULO 50 mg experienced greater improvement in SALT scores over time, as measured by SALT score change from baseline, compared to placebo at Week 24 with further increases through Week 48 (Figure 1).

Treatment effects in subgroups (age at baseline, sex, ethnic origin, region, weight, disease duration since diagnosis, duration of current episode, prior pharmacologic treatment) were consistent with the results in the overall trial population. Treatment effects in the AT/AU subgroup were lower compared to the non-AT/AU subgroup.

Improvements in regrowth of eyebrows and/or eyelashes were seen at Week 24 with LITFULO 50 mg among patients with abnormal eyebrows and/or eyelashes at baseline, with further increases seen at Week 48.

Table 8: Efficacy results of LITFULO at Week 24

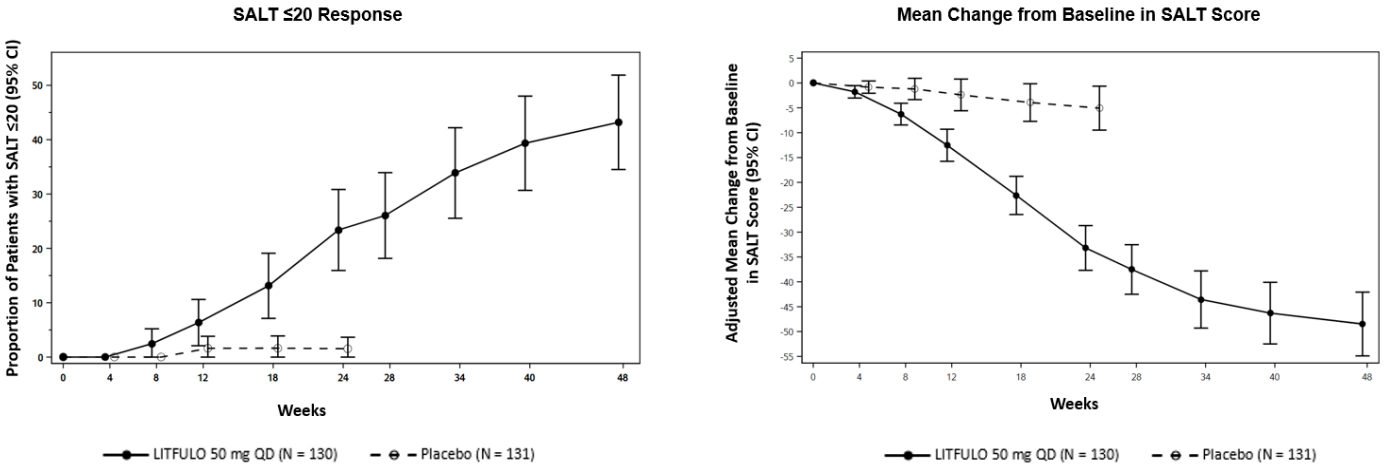
		LITFULO 50 mg QD (N = 130) % Responders	**Placebo (N = 131) % Responders**	**Difference from placebo (95% CI)**
Week 24	SALT ≤20 response[a,b]	23.0	1.6	21.4 (13.4, 29.5)
	SALT ≤10 response[b,c]	13.4	1.5	11.9 (5.4, 18.3)
	PGI-C response[d]	49.2	9.2	40.0 (28.8, 51.1)
	EBA response[e]	29.0	4.7	24.3 (14.8, 34.5)
	ELA response[f]	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; QD = once daily; SALT = severity of alopecia tool.

a. 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.
b. Statistically significant with adjustment for multiplicity.
c. SALT ≤10 responders were patients with scalp hair loss of ≤10%.
d. 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."

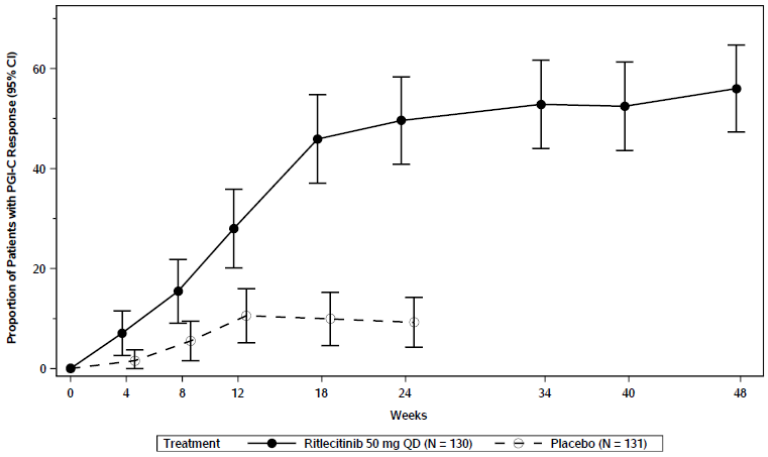
e. EBA response is defined as at least a 2-grade improvement from baseline or normal EBA score in patients with abnormal eyebrows at baseline.
f. ELA response is defined as at least a 2-grade improvement from baseline or normal ELA score in patients with abnormal eyelashes at baseline.

Figure 1: SALT ≤20 Response and Change from Baseline in SALT Score through Week 48



Abbreviations: CI = confidence interval; N = total number of patients; QD = once daily; SALT = Severity of Alopecia Tool.

Figure 2: PGI-C response through Week 48



Abbreviations: CI = confidence interval; N = total number of patients; PGI-C = patient's global impression of change; QD = once daily.

Pediatric patient population

The efficacy was evaluated in Study AA-I which included 105 patients who were 12 to <18 years of age. In this study, the efficacy results in patients 12 to <18 years are presented in Table 9 and were consistent with the results in the overall study population.

Table 9: Efficacy results of LITFULO for patients 12 to <18 years of age at Week 24

	LITFULO 50 mg QD (N = 16) % Responders	Placebo (N = 19) % Responders	Difference from placebo (95% CI)
SALT ≤20 response[a]	25.0	0	25.0 (5.5, 49.9)
SALT ≤10 response[b]	12.5	0	12.5 (-5.9, 36.4)

Abbreviations: CI = confidence interval; N = total number of patients; QD = once daily; SALT = severity of alopecia tool.

a. 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.
b. 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.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Decreased lymphocyte counts and decreased lymphoid cellularity of organs and tissues of the immune and hematolymphopoietic systems were observed in nonclinical toxicity studies and were attributed to the pharmacological properties (JAK3/TEC inhibition) of ritlecitinib. In chronic toxicity studies in dogs, there was evidence of reversible opportunistic infection secondary to immunosuppression at ≥14 times the MRHD.

Carcinogenicity: No evidence of tumorigenicity was observed in the 6-month Tg.rasH2 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 combined benign and malignant thymomas in female rats, and thyroid follicular adenomas and combined follicular adenomas and carcinomas in male rats was noted following ritlecitinib administration at exposures equal to 29 times the MRHD on an unbound AUC basis. No ritlecitinib-related thymomas or thyroid follicular adenomas were observed at exposures equal to 6.3 times the MRHD on an unbound AUC basis.

Genotoxicity: Ritlecitinib is not mutagenic in the bacterial mutagenicity assay (Ames assay). Ritlecitinib is aneugenic in vitro but 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. Ritlecitinib does not present a clinically relevant genotoxic risk.

Reproductive and Developmental Toxicology: 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 an embryo-fetal development study in pregnant rats, oral administration of ritlecitinib from gestation days 6 to 17 resulted in fetal skeletal malformations and variations and lower fetal body weights at exposures greater than or equal to 49 times the unbound AUC at the MRHD. There were no effects on embryo-fetal development at exposures equal to 16 times the unbound AUC at the MRHD.

In an embryo-fetal development study in pregnant rabbits, oral administration of ritlecitinib from gestation days 7 to 19 resulted in lower mean fetal body weights and higher incidences of post-implantation loss, 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-fetal 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 (eg, delay in vaginal patency) 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 and secondary lower number of implantation sites at exposures equal to 41 times the unbound AUC at the MRHD. There were no effects on pre- and postnatal development exposures equal to 14 times the unbound AUC at the MRHD.

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.

Nervous System Toxicity: In 9-month repeat-dose toxicity studies in dogs, reversible axonal dystrophy was noted in the CNS and PNS at doses ≥20 mg/kg/day (≥14 times the MRHD based on AUC comparison). At 40 mg/kg/day (33 times the MRHD based on AUC comparison), ritlecitinib-related axonal dystrophy caused reversible hearing loss and waveform deficits in brainstem auditory evoked potential (BAEP) testing. Additional mechanistic studies provided preliminary evidence that ritlecitinib-related axonal dystrophy may be due to off-target binding but did not identify the underlying mechanism of axonal dystrophy in dogs. 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 [see 7 WARNINGS AND PRECAUTIONS, Neurologic].

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{Pr}LITFULO^{TM} (lit-FUL-oh)

ritlecitinib capsules

Read this carefully before you start taking **LITFULO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LITFULO.**

Serious Warnings and Precautions

Serious Infections

- Taking LITFULO increases your risk of getting a serious infection. These infections can lead to hospitalization or death.
- You must not take LITFULO if you have an active infection. This is because LITFULO can make your infection worse. Before you take LITFULO, tell your healthcare professional if you have an infection including one that doesn't go away or often comes back.
- Your healthcare professional will check your risk of tuberculosis before and while you are taking LITFULO.
- Talk to your healthcare professional if you have any symptoms of an infection before you start taking LITFULO and while you are taking it. These include: fever, sweating, chills, muscle aches, cough, shortness of breath, blood in your mucus, weight loss, diarrhoea, stomach pain, burning when you urinate, urinating more often than usual, feeling very tired, sore throat.

Cancer

- LITFULO may increase your risk of getting cancer.

See "**Other warnings you should know about**" for more information.

What is LITFULO used for?

- LITFULO is used in adults and adolescents aged 12 years and older to treat severe alopecia areata.
- It is not approved for use in children below 12 years of age.

How does LITFULO work?

LITFULO reduces the activity of certain enzymes in your body called kinases. This changes the way your immune system works and reduces inflammation. This allows for hair regrowth in people with severe alopecia areata.

What are the ingredients in LITFULO?

Medicinal ingredient: ritlecitinib tosylate

Non-medicinal ingredients: Crospovidone, FD&C BLUE NO. 1, ferric oxide yellow, glyceryl dibehenate, hypromellose, lactose monohydrate, microcrystalline cellulose, titanium dioxide

LITFULO comes in the following dosage forms:

Capsules, 50 mg ritlecitinib (as ritlecitinib tosylate)

Do not use LITFULO if you:

- are allergic to ritlecitinib tosylate or to any of the other ingredients in LITFULO.
- are pregnant or are planning to become pregnant.
- are breast-feeding or are planning to breast-feed. Talk to your healthcare professional about the best way to feed your baby while taking LITFULO.
- have severe liver problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LITFULO. Talk about any health conditions or problems you may have, including if you:

- have an infection including one that doesn't go away or comes back. You must not take LITFULO if you have an active infection.
- have a weakened immune system due to a medical condition.
- take a medicine that weakens your immune system since it is not recommended to use LITFULO with these medicines.
- have recently had or plan to receive a vaccination with a live or attenuated vaccine. This includes vaccines for shingles.
- have hepatitis virus B or C infection.
- have recently travelled to regions with high rates of fungal infection.
- have low platelet count or white blood cell count.
- have or have had cancer.
- have kidney problems or have had a kidney transplant.
- have diabetes or are aged 65 years or older since people with these conditions have a higher chance of infections.
- have heart problems or have had a stroke or heart attack.
- have had a blood clot in the veins or arteries of your leg, lung or eye.
- have a skin condition called eczema.
- have difficulty digesting or breaking down some sugars, a condition called lactose intolerance.

Other warnings you should know about:

Infections: Before you take LITFULO, tell your healthcare professional if you have an infection including one that doesn't go away or often comes back. You should not take LITFULO if you have an active infection. LITFULO can make you more likely to get an~~d~~ infection or make an infection worse. Your healthcare professional will closely monitor you for infection during your treatment. They might also stop your treatment with LITFULO until the infection gets better. Talk to your healthcare professional if you have any symptoms of an infection before you start taking LITFULO or while you are taking it. These include: fever, sweating, chills, muscle aches, cough, shortness of breath, blood in your mucus, weight loss, diarrhea, stomach pain, burning when you urinate, urinating more often than usual, feeling very tired, sore throat.

- **Tuberculosis**: Before you take LITFULO, tell your healthcare professional if you have or have ever had tuberculosis (TB). Also tell them if you have recently been in close contact with someone with TB or have recently traveled to regions with high rates of TB infection. You should not take LITFULO if you have an active TB infection. Your healthcare professional may treat you for TB before you take LITFULO if you have TB or have had it before. They may also

treat you for inactive TB, a form of TB in which the TB germs are sleeping and not causing the disease, before you take LITFULO. They will monitor you for TB infection while you are taking LITFULO.

- **Herpes zoster:** Before you take LITFULO, tell your healthcare professional if you have had a herpes infection, because LITFULO may reactivate this condition.
- **Shingles:** Tell your healthcare professional if you develop a painful skin rash with blisters while you are taking LITFULO. These can be signs of shingles.

Cancer: Before you take LITFULO, tell your healthcare professional if you have or have ever had cancer. LITFULO may increase your risk of getting cancer including skin cancer. Follow your healthcare professional's advice on having your skin checked for skin cancer during treatment with LITFULO.

Blood clots: Tell your healthcare professional if you have had blood clots in your legs, lungs, eyes or have been told you are at risk of blood clots. Get emergency help right away if you have any symptoms of clots in blood vessels. These may include: swelling or pain in your leg, chest pain, shortness of breath or sudden changes to your vision (blurry vision, partial or complete loss of vision).

Heart Problems and Stroke: Before you take LITFULO, tell you healthcare professional if you have a heart problem or have had a heart attack or stroke in the past. LITFULO may increase your risk of heart attack and stroke. Get emergency help right away if you have any symptoms of a heart attack or stroke while using LITFULO. These may include new or worsening chest pain, shortness of breath, weakness in one part or on one side of your body or slurred speech.

Nervous System Problems: Tell your healthcare professional if you develop unexplained symptoms of nervous system problems while taking LITFULO as your treatment may have to be stopped**.** These include headache, burning or tingling sensation in the hands, arms, legs, or feet and altered sense of touch. Your healthcare professional will discuss with you if the treatment should be discontinued.

Blood tests and monitoring: LITFULO may decrease your white blood cell and platelet counts. Your healthcare professional will test your blood before you take LITFULO and while you are taking it. They will check for low white blood cell and low platelet counts. You will not be treated with LITFULO if these levels are low. Your healthcare professional will stop your treatment with LITFULO if your white blood cell and platelet counts are too low. Tell your healthcare professional if you develop symptoms of a low white blood cells or low blood platelets level while taking LITFULO. These include getting infections more easily, bruising or bleeding.

Birth control in women*:* You must not take LITFULO if you are pregnant or are planning to become pregnant. You must use effective birth control while you are taking LITFULO and for one month after you stop taking it. Talk to your healthcare professional about effective birth control methods.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LITFULO:

- Sumatriptan, used to treat migraine.
- Midazolam, used to treat anxiety or sleep disorders.
- Rifampin, used to treat tuberculosis.
- Medicines containing caffeine.

How to take LITFULO:

- Always take LITFULO exactly as your healthcare professional tells you to take it.

- LITFULO will be prescribed to you and managed by a healthcare professional with experience in treating alopecia areata.
- Swallow LITFULO capsules whole with water. Do not split, crush, or chew the capsules.
- You can take LITFULO with or without food.
- Check with your healthcare professional if you are not sure how to take LITFULO.
- Your healthcare professional may stop your treatment depending on your response to LITFULO after 36 weeks of treatment.

Usual dose:

Take one capsule once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much LITFULO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take LITFULO, take the dose as soon as possible. But if it is less than 8 hours before the next dose, skip the missed dose. Take the next dose at your usually scheduled time.

What are possible side effects from using LITFULO?

These are not all the possible side effects you may have when taking LITFULO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea
- Acne
- Rash
- Dizziness
- Increase in an enzyme called creatine phosphokinase, shown by blood test
- Folliculitis (inflammation of the hair follicles or pores)

LITFULO can cause abnormal blood test results. Your healthcare professional may do blood tests before you start taking LITFULO and while you take it. They will check your liver enzymes. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Infections: fever, sweating, chills, muscle aches, cough, shortness of breath, blood in your mucus, weight loss, diarrhea, stomach pain, burning when you urinate, urinating more often than usual, feeling tired, sore throat.		X	
Herpes Zoster (Shingles): a painful skin rash of fluid-filled blisters, blisters appear along a strip of skin (sometimes involving more than one body area), itching, headache, feeling tired, fever, chills.		X	
Allergic reaction: hives, rash, swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.			X
UNCOMMON			
Lymphopenia (low white blood cells): get infections more easily.		X	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store LITFULO at room temperature (15°C to 30°C). Keep in original package. Keep out of reach and sight of children.

If you want more information about LITFULO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.
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