CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215830
PDUFA Goal Date	June 23, 2023
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Reviewer Name(s)	Sarah K. Holman, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 20, 2023
Subject	Evaluation of Need for a REMS
Established Name	Ritlecitinib
Trade Name	Litfulo
Name of Applicant	Pfizer Inc.
Therapeutic Class	Kinase inhibitor
Formulation(s)	Oral capsule
Dosing Regimen	50 mg orally once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Litfulo (ritlecitinib) is necessary to ensure the benefits outweigh its risks. Pfizer Inc. submitted a New Drug Application (NDA) 215830 for ritlecitinib with the proposed indication: (b) (4) During the course of the review, the Agency revised the indication to the following: for the treatment of severe alopecia areata in adults and adolescents 12 years and older. The Agency also added limitations of use to the labeled indication: Not recommended for use in combination with other Janus Kinase inhibitors, biologic immunomodulators, cyclosporine, or other potent immunosuppressants. At the time of this review, labeling negotiations were ongoing. The Applicant did not submit a proposed REMS or risk management plan with this application. The Applicant's proposed labeling includes a Boxed Warning for serious infections and malignancy and a Medication Guide.

DRM and the Division of Dermatology and Dentistry (DDD) have determined that a REMS is not needed to ensure the benefits of ritlecitinib outweigh its risks. The benefit of treatment of alopecia areata with ritlecitinib was demonstrated in a Phase 2b/3, double-blind, placebo-controlled trial. In the ritlecitinib 50 mg treatment group, there was a statistically significantly greater proportion of subjects with a Severity of Alopecia Tool Score ≤ 20 at Week 24 compared with placebo. Treatment effects were similar in adults and adolescents. Although the subgroup of subjects with non-AT/AU had a greater response rate compared with subjects with AT/AU, both groups demonstrated a greater response than placebo.

The risks associated with ritlecitinib include serious infections, malignancies, thrombosis, hematologic abnormalities, hepatic enzyme elevations, and creatine phosphokinase (CPK) elevations. The labeling for ritlecitinib will communicate the risks of serious infections, mortality, malignancies, major adverse cardiovascular events, and thrombosis with a Boxed Warning. This Boxed Warning is consistent with the Boxed Warnings for agents in the JAK inhibitor class approved for inflammatory conditions including alopecia areata. The risk of laboratory abnormalities (including hematologic abnormalities, liver enzyme elevations, and CPK elevations) will be communicated in Section 5, Warnings and Precautions. Labeling will also include a Medication Guide to communicate risks to patients. The likely prescribing population should be familiar with the risks and appropriate monitoring and management as there are several JAK inhibitors FDA-approved for dermatologic conditions including atopic dermatitis and alopecia areata.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Litfulo (ritlecitinib) is necessary to ensure the benefits outweigh its risks. Pfizer Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 215830 for ritlecitinib with the proposed indication for the treatment of alopecia areata, (b) (4) This application is under review in the Division of Dermatology and Dentistry. The Applicant did not submit a proposed REMS or risk management plan

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with this application. The Applicant's proposed labeling includes a Boxed Warning for serious infections and malignancy, and a Medication Guide to convey risks to patients.

2. Background

2.1. Product Information

Litfulo (ritlecitinib), a new molecular entity,[a] is a kinase inhibitor. Ritlecitinib irreversibly inhibits Janus kinase (JAK) 3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family by blocking the adenosine triphosphate binding site. Ritlecitinib also inhibits cytokine induced Signal Transducers and Activators of Transcription (STAT) phosphorylation mediated by JAK3-dependent receptors and signaling of immune receptors dependent on TEC kinase family members. It is unknown how inhibition of specific JAK or TEC family enzymes relates to the therapeutic effectiveness of ritlecitinib. Ritlecitinib was originally submitted as a JAK3/TEC kinase family inhibitor, however the Agency revised the therapeutic class to kinase inhibitor as ritlecitinib targets several different kinases.[2] Ritlecitinib is proposed for the treatment of alopecia areata (b) (4)

During the course of the review, the Agency revised the indication to the following: for the treatment of severe alopecia areata in adults and adolescents 12 years and older. The Agency also added limitations of use to the labeled indication: Not recommended for use in combination with other Janus Kinase inhibitors, biologic immunomodulators, cyclosporine, or other potent immunosuppressants.[3] At the time of this review, labeling negotiations were ongoing.

Ritlecitinib is proposed for chronic use[b] and will be supplied as a 50 mg capsule to be taken orally once daily in an outpatient setting. Proposed dosing includes screening for viral hepatitis, updating immunizations according to current immunization guidelines, avoidance in patients with active tuberculosis (TB), and avoidance in those with an absolute lymphocyte count (ALC) of <500/mm^3 or a platelet count 100,000/mm^3. In those with latent TB or who are at high risk for TB, preventative therapy should be initiated prior to starting ritlecitinib. Treatment with ritlecitinib should be discontinued if the platelet count falls below (b) (4) /mm^3 and should be interrupted in the setting of serious or opportunistic infections or if the ALC falls below 500/mm^3. Ritlecitinib was granted breakthrough therapy designation in July 2018 which was rescinded in November 2022. Ritlecitinib is not currently approved in any jurisdiction.

There are currently seven JAK-inhibitors that are FDA-approved in the United States; see Appendix 10.2 for a table of FDA-approved JAK inhibitors. Ritlecitinib is expected to have similar safety risks to the JAK inhibitor class given overlapping mechanism of action. At this time, none of the JAK inhibitors are approved with a REMS, however, risk mitigation strategies for communicating the risks of the JAK inhibitor class have evolved over time. Xeljanz (tofacitinib) was approved on November 6,

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2012, for the treatment of moderate to severe active rheumatoid arthritis. Xeljanz was approved with a REMS that was comprised of a Medication Guide and communication plan (CP) to mitigate the risk of serious infections, malignancies, lympho-proliferative disorders, increased cholesterol, and low blood cell counts. The REMS was eliminated in February 2016 after the Agency determined that it was no longer necessary because the activities had been completed and the most recent REMS assessment demonstrated the CP REMS had met its goals.[4,5]

Based on data received from postmarketing studies of tofacitinib and the issuance of a Safety Labeling Change Notification Letter, labeling for the JAK inhibitors approved for inflammatory conditions was revised in December 2021.[6-8] The safety labeling changes were primarily based on data from postmarketing studies for tofacitinib; however, the Agency determined these risks to be a class effect for JAK inhibitors approved for inflammatory conditions. The Boxed Warnings and Warning/Precautions sections for these agents were revised to include information about the risk of MACE, malignancy, thrombosis, and mortality. Ritlecitinib is proposed with Boxed Warnings for serious infections and malignancy.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215830 relevant to this review:

- **07/31/2018**: Breakthrough therapy designation granted for IND 131503.
- **06/24/2022**: NDA 215830 submission for the treatment of alopecia areata (b) (4)
- **11/29/2022**: Breakthrough therapy designation rescinded for IND 131503 based on another drug, baricitinib, gaining traditional approval in June 2022 for the same indication.
- **12/05/2022**: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ritlecitinib.[9]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Alopecia areata (AA) is a chronic, relapsing, immune-mediated disease that targets anagen hair follicles and causes nonscarring hair loss.[10] Patients with AA most commonly present with discrete, smooth patches of alopecia on the scalp but may also experience hair loss of the eyebrows, eyelashes, and extremities. In the most severe cases, patients experience loss of all scalp hair known as alopecia totalis (AT) or all body hair known as alopecia universalis (AU). Nail involvement occurs in 10-20% of patients and is more common in severe disease. While spontaneous regrowth of hair is common in patients with limited patchy hair loss, patients frequently experience disease recurrence. In more severe cases, AA may persist indefinitely or progress to AT or AU.[10] Overall disease onset peaks at age 25-29 years; however in children, the mean age of onset is between 5 and 10 years.[11,12]

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In addition to the clinical manifestations of the disease, patients may also experience significant psychosocial effects including reduced quality of life, anxiety, depression, unemployment, and social phobia.[13-15] In children, AA can be associated with low self-esteem, failure to achieve in school, social withdrawal, and behavior changes.[16,c] In the United States, the lifetime risk of AA is approximately 2% with an estimated prevalence of 1 in 500-1000 people.[10,17] There are approximately 700,000 people in the United States with AA and approximately 300,000 people with moderate to severe disease.[18,d]

3.2. Description of Current Treatment Options

There is currently one FDA-approved pharmacologic treatment for AA, baricitinib, approved in June 2022. Baricitinib is a JAK inhibitor which is administered orally once daily. Baricitinib is labeled with Boxed Warnings for serious infections, mortality, malignancies, major adverse cardiovascular events, and thrombosis.[19] Baricitinib is recommended by some experts as the preferred JAK inhibitor for treatment of AA in patients with extensive (>50% hair loss) or refractory disease given the large, randomized trials supporting its efficacy.[20]

Treatment options for AA which have been used off-label include corticosteroids (intralesional, topical, or systemic), contact immunotherapy, minoxidil, anthralin, methotrexate, and off-label use of JAK inhibitors including oral tofacitinib and oral ruxolitinib.[20] There is lack of consensus regarding the preferred option for management of AA. The Alopecia Areata Consensus of Experts study, an international consensus statement on various treatments for AA, recommends treatment selection based on patient age, disease duration, and extent of hair loss. In general, intralesional and topical corticosteroids are the preferred treatment options, although JAK inhibitors would be a preferred systemic therapy if all treatments were equally reimbursed.[21] Intralesional and topical corticosteroids may both cause skin atrophy, while topical corticosteroids additionally may cause pruritis, telangiectasias, acne, and striae.[22] Treatment with oral corticosteroids is generally limited to short courses due to safety concerns associated with chronic use including adrenal suppression, effects on bone growth and integrity, and worsening of hypertension and diabetes mellitus.[22] Given variable effectiveness of available treatment options for AA and potential risks with therapy, there is an unmet medical need for treatment of AA.

Non-pharmacologic treatment for AA includes cosmetic options including wigs, hairpieces, protein powders, eyebrow tattooing, and false eyelashes. Treatment may also include referral for psychosocial support such as support groups, counseling, and/or psychiatric treatment.[20]

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

4. Benefit Assessment

The primary evidence for efficacy of ritlecitinib for the treatment of alopecia areata is supported by a single phase 2b/3 pivotal trial, Study B7981015 (National Clinical Trial [NCT] 03732807, hereafter referred to as ALLEGRO-2b/3).[23] ALLEGRO-2b/3 was a randomized, double-blind, placebo controlled, dose-ranging study which evaluated 718 adults and adolescents ≥ 12 years of age (ritlecitinib group=587, placebo group=131) with alopecia areata and 50% or greater scalp hair loss without evidence of terminal scalp hair regrowth within the previous 6 months.[23,e] Subjects were randomized to one of five ritlecitinib treatment regimens (including arms with and without loading doses) or placebo.[f] The proposed dose of ritlecitinib is 50 mg by mouth once daily without a loading dose (hereafter referred to as the ritlecitinib 50 mg treatment arm), therefore the efficacy of this treatment regimen compared with placebo will be the focus of this review (ritlecitinib group=130, placebo group=131).[g]

The study population in ALLEGRO-2b/3 had a mean age of 34 years with 85.4% of subjects ≥18 years of age and 14.6% of subjects aged 12 to <18 years. Most subjects were female (62.1%) and White (68%). The mean baseline Severity of Alopecia Tool (SALT)[h] score ranged from 88.3 to 93 across treatment groups and 46% of subjects were classified as AT/AU. The baseline demographics were well-balanced between study groups.[23]

The primary endpoint was the proportion of subjects with an absolute SALT Score ≤20 at Week 24. The ritlecitinib 50 mg daily group had a statistically significant greater proportion of subjects with a SALT ≤ 20 at Week 24 compared with placebo as outlined in Table 1 below.[23] Treatment effects in adults and adolescents were similar and consistent with the results in the overall trial population. Although the subgroup of subjects with non-AT/AU had a greater response rate compared with subjects with AT/AU

[e] ALLEGRO-2b/3 consisted of two study periods. The first study period (weeks 0-24) was a double-blind, placebo-controlled dose-ranging study. The second study period (weeks 25-48) was a 24-week extension in which subjects receiving placebo were switched to ritlecitinib.

[f] Subjects were randomized to one of five doses of ritlecitinib or placebo. Ritlecitinib regimens were with or without a loading dose of 200 mg by mouth daily for the first 4 weeks: 200/50 mg, 200/30 mg, 50 mg, 30 mg, 10 mg. In the two treatment arms that received loading doses (200/50 mg, 200/30 mg), the loading dose was followed by 20 weeks of maintenance therapy of either ritlecitinib 50 mg or 30 mg. In the three treatment arms without loading doses, the participants received either ritlecitinib 50 mg, 30 mg, or 10 mg by mouth daily for 24 weeks.

[g] The 50 mg dose of ritlecitinib was selected as the proposed marketed dose given lack of sustained additional benefit of the 200 mg loading dose on long-term efficacy compared to the 50 mg treatment arm without a loading dose, and higher incidence of some adverse effects with a loading dose (hematologic abnormalities, tinnitus, nausea, folliculitis, respiratory infections, urinary infections, and dizziness).

[h] The Severity of Alopecia Tool (SALT) is a standard measure for quantitative assessment of alopecia areata severity based on scalp hair loss. SALT assesses hair loss by scalp quadrant and assigns a score using the sum of percentage of hair loss in the four quadrants. A SALT score of 0 indicates no scalp hair loss, and a SALT score of 100 indicates complete scalp hair loss.

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(36.2% vs 7.3% with SALT≤ 20 response, respectively), both groups demonstrated a greater response than placebo. Secondary endpoints were not adequately adjusted for multiplicity and will not be addressed in this review or included in the labeling.

Table 1. Proportion of Subjects with SALT ≤ 20 Response at Week 24[23]

	Placebo N=131	Ritlecitinib 50 mg daily N=130
% Responders	1.5	23.4
Difference from Placebo (95% CI)	21.9 (14.65, 30.23)	
p-value	<0.0001	

The Clinical Reviewer concluded that the Applicant provided evidence of effectiveness of ritlecitinib based on the results of ALLEGRO-2b/3.[i,2]

5. Risk Assessment & Safe-Use Conditions

The primary safety population for ritlecitinib consists of all subjects in the randomized population who received ritlecitinib 50 mg in the pivotal phase 2b/3 trial, ALLEGRO-2b/3. Study B7981032 (NCT04006457, hereafter referred to as ALLEGRO-LT) is a phase 3, open-label, multi-center, ongoing study evaluating the long-term safety and tolerability of ritlecitinib in adults and adolescents ≥ 12 years of age with alopecia areata which provides additional supportive safety data.[24]

The primary safety population includes 130 subjects randomized to ritlecitinib 50 mg vs 131 subjects randomized to placebo. The treatment duration for the majority of subjects ranged from 40 to 49 weeks. The most common adverse events (≥ 1% of ritlecitinib group and a higher rate than placebo group) were headache, diarrhea, acne, rash, urticaria, folliculitis, pyrexia, atopic dermatitis, dizziness, increased blood creatine phosphokinase, herpes zoster, decreased red blood cell count, and stomatitis.[3,24] Two participants receiving ritlecitinib 50 mg permanently discontinued the placebo-controlled study early due to urticaria.

Two additional study pools are used to summarize clinical safety and are described below.[24]

- PCPAA: Placebo-Controlled Pool (Alopecia Areata)
  - This cohort includes subjects with alopecia areata who were randomized and received up to 24 weeks of placebo-controlled treatment and includes studies B7931005, B7981015, and B7981037
  - There were 881 subjects randomized and 345 are included in the all 50 mg dose group (combined treatment group for 200/50 mg and 50 mg dose groups)

[i] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

- PCPAAV: Placebo-Controlled Pool (Alopecia Areata and Vitiligo)
    - This cohort includes subjects with alopecia areata or vitiligo who were randomized and received up to 24 weeks of placebo-controlled treatment and includes studies B7931005, B7981015, B7981019, and B7981037
    - There were 1245 subjects randomized and 544 are included in the all 50 mg dose group (combined treatment group for 200/50 mg 100/50 mg, and 50 mg dose groups)
    - The study in vitiligo is considered relevant for the evaluation of safety in AA given similarities in the AA and vitiligo populations (pathophysiology, age of patients, comorbidities of patients), similar ritlecitinib dosing regimens, and similar safety monitoring

5.1. Deaths

There were no deaths in the pivotal trial, ALLEGRO-2b/3, up for 48 weeks which includes the placebo-controlled and extension study periods. In the long-term, open-label study, ALLEGRO-LT, there were two deaths in subjects receiving ritlecitinib. One subject, a 64-year-old female, experienced a serious adverse event[j] (SAE) of breast cancer of the right breast on Study Day 90. The subject died due to breast cancer 8 months after study discontinuation. The other subject, a 51-year-old female, experienced SAEs of acute respiratory failure and cardiorespiratory arrest on Study Day 234 resulting in death. The subject's medical history included asthma and smoking. Neither of the deaths were attributed to treatment with ritlecitinib by the Applicant or the Clinical Reviewer.[2,24]

5.2. Serious Adverse Events

5.2.1. Serious Adverse Events

In the placebo-controlled period of the pivotal trial, ALLEGRO-2b/3, there were no SAEs in the ritlecitinib 50 mg treatment arm. In the 200/50 mg treatment arm, there were 4 subjects with 5 SAEs (1.9%); 2 subjects with serious infections, 1 subjects with invasive lobular breast cancer, and 1 subject with spontaneous abortion.[k,24] There were 3 subjects with 3 SAEs in the placebo group (2.2%) which included spontaneous abortion, conversion disorder, and heavy menstrual bleeding.[24] In the 24-week extension period of the pivotal trial, there was 1 additional subject receiving ritlecitinib 50 mg with an SAE of breast cancer and 1 subject with an SAE of pulmonary

[j] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[k] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

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embolism. See Sections 5.2.2, 5.2.3 and 5.2.4 below for further discussion of serious infections, malignancy, and thromboembolic events, respectively.

The labeling for ritlecitinib will communicate the risks of serious infections, mortality, malignancy, MACE, and thrombosis with a Boxed Warning. This Boxed Warning is consistent with the Boxed Warnings for other agents in the JAK inhibitor class approved for inflammatory conditions including alopecia areata.

5.2.2. Serious Infections

In the PCPAA pool, there were no serious infections[l] among participants who received ritlecitinib 50 mg or placebo.[24] In the 200/50 mg treatment arm, there were serious infections in 2 participants (0.9%). One participant experienced sepsis and empyema and the other participant experienced appendicitis, both of which recovered from the infections. In the PCPAAV pool ritlecitinib all 50 mg dose group, the serious infections that occurred in more than 1 participant included appendicitis (4 participants), COVID-19 (2 participants), and COVID-19 pneumonia (2 participants). Per protocol, all serious infections required discontinuation from the clinical trial. The Clinical Reviewer concluded that there does not appear to be increased risk of serious infection with longer duration of treatment.[2]

Opportunistic infections

There were no cases of active tuberculosis (TB) in the safety pool.[24] In the PCPAA pool, herpes zoster infections were reported for 2 (1.5%) subjects in the ritlecitinib 50 mg group compared with 0 subjects in the placebo group.[24] Neither of the infections were severe adverse events. In the PCPAAV pool, there were 2 participants who received ritlecitinib 50 mg with a confirmed opportunistic infection of multi-dermatomal herpes zoster, one participant receiving ritlecitinib 200/50mg and the other receiving ritlecitinib 50mg.

The Clinical Reviewer recommends the risk of serious bacterial, fungal, viral, and opportunistic infections including tuberculosis be communicated in labeling, Boxed Warning and Section 5: Warnings and Precautions.[2,3] Labeling will include the recommendation that patients should be closely monitored for signs and symptoms of infection during and after treatment with ritlecitinib, and treatment should be interrupted if serious infection occurs until the infection is controlled. Ritlecitinib should not be given to patients with active TB, patients should be tested for and treated for latent TB before treatment, and patients should be monitored for active TB during treatment.[3]

[l] Serious infections were defined as infections requiring parenteral antimicrobial therapy, hospitalization, or reported as SAE and classified in the systemic organ class of infections/infestations.

5.2.3. Malignancy and Lymphoproliferative Disorders

In the PCPAA pool, one subject receiving ritlecitinib 200/50 mg was adjudicated with an SAE of invasive lobular breast cancer.[24] In the 24-week extension period of the pivotal trial, ALLEGRO-2b/3, one additional subject receiving ritlecitinib 50 mg was adjudicated with an SAE of breast cancer. In the long-term extension study, ALLEGRO-LT, 5 subjects were adjudicated with SAEs of malignancy: 2 subjects with breast cancer, 1 subject with papillary thyroid cancer, 1 subject with testis cancer, and 1 subject with malignant melanoma.[24] No cases of non-malignant skin cancers (NMSCs) were reported in the PCPAA pool, however 3 subjects in the long-term extension study, ALLEGRO-LT were reported with adverse events of NMSC; 2 subjects with basal cell carcinoma and 1 subject with Bowen's disease.[24]

The Clinical Reviewer recommends the risk of malignancy and lymphoproliferative disorders be communicated in labeling, Boxed Warning and Section 5: Warnings and Precautions.[2,3] Labeling will include the recommendation to consider the risks and benefits of ritlecitinib treatment in patients with a known malignancy other than successfully treated NMSC or cervical cancer; and for periodic skin examination for patients at increased risk for skin cancer.[3]

5.2.4. Thromboembolic Events

In the 24-week extension period of the pivotal trial, ALLEGRO-2b/3, one subject experienced an SAE of bilateral pulmonary embolism (PE) on Study Day 169.[24] The subject, a 54-year-old female, was receiving ritlecitinib 50 mg and had a past medical history of obesity, monoclonal gammopathy, sleep apnea syndrome, hypertension, and recent COVID-19 infection. The PE was considered related to the study treatment by the Applicant. There were no adverse events meeting criteria for deep venous thrombosis in the ritlecitinib clinical development program.

The Clinical Reviewer recommends the risk of thromboembolic events be communicated in labeling, Boxed Warning and Section 5: Warnings and Precautions.[2,3] Labeling will include the recommendation that ritlecitinib be avoided in patients who may be at increased risk of thrombosis and treatment should be interrupted if symptoms of thrombosis occur.[3]

5.3. Adverse Events of Special Interest

5.3.1. Laboratory Abnormalities

Lymphopenia and Thrombocytopenia

In PCPAAV pool, a decrease in mean platelet count of approximately 35,000/mm^3 was observed for the ritlecitinib 50 mg group by Week 2 which remained consistently low through Week 24.[24] There were no subjects with platelet counts below 50,000/mm^3 or which met criteria for study treatment discontinuation. Additionally, a decrease in the mean absolute lymphocyte count (ALC) was reported in the initial 2-4 weeks of treatment which remained lower than baseline levels at Week 24, with a greater decrease in ALC observed with higher maintenance doses and

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loading doses.[24] For the ritlecitinib 50 mg group, the mean change from baseline in ALC was a decrease of 270/mm^3 and one subject experienced a Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 event (<200/mm^3). The subject did not receive any treatment, the study drug was continued, and the lymphopenia resolved.[24]

Liver Enzyme Elevations

In PCPAA pool ritlecitinib all 50 mg dose group, increases were reported in alanine transaminase (ALT) at >3x (0.9%) and >5x (0.3%) the upper limit of normal (ULN), aspartate transaminase (AST) at >3x (0.6%) and >5x (0.6%) the ULN, and total bilirubin at >2x (0.6%) ULN compared to 0% with placebo.[24] In the PCPAAV pool, two subjects receiving ritlecitinib 50 mg were permanently discontinued from the study drug due to elevated ALT or AST (1 subject each). There were no potential Hy's Law cases.[24]

Creatine Phosphokinase Elevations

In the PCPAAV pool, the proportion of subjects with adverse events of increased blood creatine phosphokinase (CPK) was higher with ritlecitinib 50 mg (2.5%) compared to placebo (0.7%).[24] No adverse events of rhabdomyolysis were reported in any treatment groups and no subjects receiving ritlecitinib 50 mg discontinued from the trial due to CPK elevation. Two subjects receiving ritlecitinib 200/50 mg and one subject receiving placebo discontinued study drug due to elevated CPK greater than 3x the ULN.[24]

The Clinical Reviewer recommends the risk of laboratory abnormalities including decreased lymphocytes and platelets, liver enzyme elevations, and CPK elevations be communicated in labeling, Section 5: Warnings and Precautions.[2,3] Recommendations regarding not initiating ritlecitinib in patients with lymphopenia or thrombocytopenia, and interrupting or discontinuing therapy should lymphopenia or thrombocytopenia occur will be communicated in Section 2, Dosage and Administration, of labeling.[3]

6. Expected Postmarket Use

Ritlecitinib is mostly likely to be prescribed and self-administered in the outpatient setting for treatment of alopecia areata. The most likely prescribers are dermatologists who are experienced with managing patients with alopecia areata. These prescribers are likely familiar with the risks associated with the JAK inhibitor drug class given there are other agents in this class approved for treatment of dermatologic conditions including alopecia areata and atopic dermatitis.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ritlecitinib beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ritlecitinib. During the course of the review, the Agency revised the indication to the following: for the treatment of severe alopecia areata in adults and adolescents 12 years and older. The Agency also added limitations of use to the labeled indication: Not recommended for use in combination with other Janus Kinase inhibitors, biologic immunomodulators, cyclosporine, or other potent immunosuppressants.[3]

Alopecia areata (AA) is a chronic, relapsing, immune-mediated disease that targets anagen hair follicles and causes nonscarring hair loss. In the most severe cases, patients experience loss of all scalp hair or all body hair and may also experience significant psychosocial effects. There is currently one FDA-approved pharmacologic treatment for AA, baricitinib, an oral JAK inhibitor. Other treatment options for AA which have been used off-label include corticosteroids, contact immunotherapy, minoxidil, anthralin, methotrexate, and off-label use of other JAK inhibitors, however these therapies have variable effectiveness and potential risks representing an unmet medical need.

The benefits of treatment of alopecia areata with ritlecitinib were demonstrated in a Phase 2b/3, double-blind, placebo-controlled trial. In the ritlecitinib 50 mg treatment group, there was a statistically significantly greater proportion of subjects with a SALT ≤ 20 at Week 24 compared with placebo. Treatment effects were similar in adults and adolescents. Although the subgroup of subjects with non-AT/AU had a greater response rate compared with subjects with AT/AU, both groups demonstrated a greater response than placebo.

The risks associated with ritlecitinib include serious infections, malignancies, thrombosis, hematologic abnormalities, hepatic enzyme elevations, and CPK elevations. Ritlecitinib was originally submitted with a Boxed Warning for serious infections and malignancies. Given the overlap in mechanisms of action on inhibition of JAK, ritlecitinib is expected to have similar safety risks to the JAK inhibitor class. Any differential effects on efficacy and safety based on inhibition of specific JAK enzymes is not currently known.[2] The clinical reviewer concluded that the adverse reactions observed in subjects with AA treated with ritlecitinib was consistent with the safety profile of other JAK inhibitor products.[2] During the course of the review, the Boxed Warning was revised to communicate the risks of serious infections, mortality, malignancy, MACE, and thrombosis consistent with the Boxed Warnings for other agents in the JAK inhibitor class approved for inflammatory conditions including alopecia areata. The risk of laboratory abnormalities (including hematologic abnormalities, liver enzyme elevations, and CPK elevations) will be communicated in Section 5, Warnings and Precautions. Recommendations regarding not initiating ritlecitinib in patients with lymphopenia or thrombocytopenia, and interrupting or discontinuing therapy should serious infection, opportunistic infection, lymphopenia, or thrombocytopenia occur will be communicated in Section 2, Dosage and Administration, of labeling.[3] Labeling will also include a Medication Guide to communicate risks to patients.

Based on the data currently available, this reviewer is not recommending a REMS for the management of the risks of ritlecitinib. The risks of ritlecitinib are similar to the risks of approved therapies in the JAK inhibitor drug class and will be communicated through a Boxed Warning and Warnings and Precautions. No risk mitigation strategies beyond labeling are used to communicate the risks for any agent within the

JAK inhibitor drug class. Baricitinib, which is FDA-approved for treatment of alopecia areata, has similar risks to ritlecitinib labeled in Section 5, Warnings and Precautions, including serious infections, tuberculosis, malignancies, liver enzyme elevations, CPK elevations, gastrointestinal perforations, hematologic abnormalities (lymphopenia, anemia, neutropenia), and lipid abnormalities.[19] There are several JAK inhibitors approved for dermatologic conditions including atopic dermatitis and alopecia areata. Therefore, prescribers of ritlecitinib should be familiar with these risks and the appropriate monitoring and management and are expected to be appropriately informed about the risks through labeling which includes a Boxed Warning.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety and proposed risk management approach for ritlecitinib is similar to other agents within the JAK inhibitor class approved for inflammatory conditions including alopecia areata. We expect healthcare providers to be appropriately informed about the risks through labeling which includes a Boxed Warning. Given there are several JAK inhibitors approved for dermatologic conditions including atopic dermatitis and alopecia areata, prescribers of ritlecitinib should be familiar with these risks and the appropriate monitoring and management. At the time of this review, labeling negotiations were ongoing. Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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10.2. Table 2. FDA-Approved JAK Inhibitors[25]

Name (generic), Approval Year	Indications[m]	Formulation	Risk Management Approaches/Boxed Warning, Medication Guide
Jakafi (ruxolitinib), 2011	• Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-versus-host disease • Chronic graft-versus-host disease	Oral tablet	**Warnings and Precautions** include: thrombocytopenia, anemia, and neutropenia; risk of infection; symptom exacerbation following interruption or discontinuation of therapy; non-melanoma skin cancer; lipid elevations; MACE; thrombosis; secondary malignancies
Xeljanz and Xeljanz XR (tofacitinib), 2012	• Rheumatoid Arthritis • Psoriatic Arthritis • Ulcerative Colitis • Polyarticular Course Juvenile Idiopathic Arthritis • Ankylosing spondylitis	Oral tablet, extended-release tablet, and oral solution	**REMS history**: Approved with REMS consisting of Medication Guide, Communication Plan, and timetable for submission of assessments for risk of serious infections, malignancies, lympho-proliferative disorders, increased cholesterol, low blood cell counts. REMS released in 2016. **Boxed Warning:** serious infections, mortality, malignancies, major adverse cardiovascular events (MACE), and thrombosis **Warnings and Precautions** (in addition to those described in the Boxed Warning) include: hypersensitivity; hepatic impairment; interstitial lung disease; need to avoid live vaccines during treatment; need to avoid combination with strong immunosuppressive medications and biologic disease-modifying antirheumatic drugs **Medication Guide**
Olumiant (baricitinib), 2018	• Rheumatoid Arthritis • **Alopecia areata** • COVID-19, hospitalized patients	Oral tablet	**Boxed Warning:** serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those described in the Boxed Warning) include: gastrointestinal (GI) perforations; laboratory abnormalities (neutropenia, lymphopenia, anemia, liver enzyme elevations, lipid

[m] This table does not capture the full indication statement but aims to provide a high-level overview of the diseases each JAK inhibitor is indicated to treat. See full prescribing information for more details.

			elevations); need to avoid live vaccines during treatment; and hypersensitivity **Medication Guide**
Rinvoq (upadacitinib), 2019	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Atopic dermatitis • Nonradiographic axial spondyloarthritis • Ulcerative colitis • Crohn's disease	Oral tablet	**Boxed Warning**: serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those described in the Boxed Warning) include gastrointestinal (GI) perforations; laboratory parameters (neutropenia, lymphopenia, anemia, lipids, liver enzyme elevations); embryofetal toxicity; hypersensitivity; and need to avoid live vaccines during treatment **Medication Guide**
Inrebric (fedratinib), 2019	• Myelofibrosis	Oral capsule	**Boxed Warnin**g: Encephalopathy including Wernicke's **Warnings and Precautions** (in addition to those described in the Boxed Warning) include: anemia and thrombocytopenia; GI toxicity; hepatic toxicity; amylase and lipase elevation; MACE; thrombosis; and secondary malignancies **Medication Guide**
Opzelura, (ruxolitinib), 2021	• Atopic dermatitis	Topical cream	**Boxed Warning:** serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those described in the Boxed Warning) include: thrombocytopenia, anemia, and neutropenia; lipid elevations **Medication Guide**
Cibinqo (abrocitinib), 2022	• Atopic dermatitis	Oral tablet	**Boxed Warning:** serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those described in the Boxed Warning) include: thrombocytopenia and lymphopenia; lipid elevations **Medication Guide**
Vonjo (pacritinib), 2022	• Myelofibrosis	Oral capsule	**Warnings and Precautions** include: QTc prolongation; MACE; GI toxicity; thrombocytopenia; hemorrhage; serious infections; secondary malignancy; thrombosis

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