09-J4000-57

Original Effective Date: 10/01/23

Reviewed: 11/13/24

Revised: 01/01/25

Subject: Ritlecitinib (Litfulo) Capsule

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Ritlecitinib (Litfulo) is an oral Janus kinase (JAK) inhibitor approved by the United States (US) Food and Drug Administration (FDA) in June 2023 for “the treatment of severe alopecia areata in adults and adolescents 12 years and older”. Ritlecitinib is the second JAK inhibitor to be approved by the FDA for the treatment of alopecia areata (AA); the first being baricitinib (Olumiant) in June 2022. Of note, as of August 2023, baricitinib is only approved for use in adults with AA, while ritlecitinib is approved for use in adolescents and adults. Ritlecitinib irreversibly inhibits JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family, with no activity on JAK1, JAK2, or TYK2 receptors. It is the first FDA-approved JAK3/TEC selective inhibitor. Various JAK inhibitors are still in development, and each has a unique inhibitory profile among the various JAK proteins. The clinical significance in terms of safety and efficacy of the different affinity profiles among the JAK inhibitors has yet to be determined. Ritlecitinib is also being evaluated in the TRANQUILLO Phase 3 trial for vitiligo. Like other JAK inhibitors, ritlecitinib includes a Boxed Warning regarding risk of serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis.

DERMATOLOGICAL DISORDERS

Alopecia Areata

Alopecia areata (AA) is a chronic, inflammatory disorder that affecting hair follicles and sometimes nails. Initial presentation generally involves patches of hair loss on the scalp, but any hair-bearing skin may be involved. Short broken hairs, also known as exclamation, point hairs, may be seen around the margins of the patches. The hair follicles in the growth phase prematurely transition to the non-proliferative involution and resting phases. This leads to hair shedding and inhibition of hair growth. The integrity of hair follicles is preserved, allowing for the potential regrowth of hair even in longstanding disease. Roughly 34 to 50% of patients will spontaneously recover within a year from symptom onset. AA often remits in patients with almost all patients experiencing multiple episodes of the disease, and roughly 14

to 50% of patients will progress to total scalp hair loss, known as alopecia totalis (AT), or total loss of scalp and body hair, known as alopecia universalis (AU). Severity at initial presentation is a strong predictor of long-term outcomes of the disease, with more severe disease progressing to AT or AU. Diagnosis is based off of clinical presentation and patient history. Other causes of alopecia need to be ruled out, and some patients may require a biopsy for diagnosis.

The management of AA involves counseling, and potentially antidepressants, due to the psychological effects associated with hair loss. Pharmacologic treatments are often temporary and do not alter the long-term course of the disease. Spontaneous remission rates also make it difficult to assess treatment efficacy, especially in patients with mild disease. Very potent topical corticosteroids have been used to treat patchy AA spots, but there is limited evidence to support long-term use. Intralesional corticosteroids are also an option for patchy AA spots and have shown more sustained hair growth. Systemic corticosteroids are generally reserved for patients with more extensive hair loss, but adverse effects tend to limit duration of use. Hair loss frequently recurs when these treatments are stopped. Conventional systemic immunomodulators and JAK inhibitors are often used for patients with disease that is refractory to corticosteroids and topical immunotherapy.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of ritlecitinib (Litfulo) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "5"):

1. **ONE** of the following ("a", "b", or "c"):
    a. The member has been treated with ritlecitinib (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with ritlecitinib (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
    c. **BOTH** of the following ('i" and "ii"):
        i. Ritlecitinib will be used for the treatment of an indication listed in Table 1, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following if the member has an FDA-approved indication ("I" or "II"):
            I. The member's age is within FDA labeling for the requested indication for ritlecitinib
            II. There is support for using ritlecitinib for the member's age for the requested indication
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist for alopecia areata) or the prescriber has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA-labeled contraindications to ritlecitinib

4. Member will **NOT** be using ritlecitinib in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
5. **ANY** of the following ("a", "b", "c", or "d"):
    a. The dosage does not exceed 50 mg once daily
        - QL: 28 capsules/28 days (one per day)
    b. The member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
        ii. **ALL** of the following ("1", "2", and "3"):
            1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
            2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
            3. **EITHER** of the following ("a" or "b"):
                a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
                b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)
    c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
        ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)
    d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):
        i. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
        ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Approval duration: 12 months

Table 1

Diagnosis	Criteria
Alopecia areata (AA)	**BOTH** of the following: 1. Member has a diagnosis of severe alopecia areata **AND** 2. Member has at least 50% scalp hair loss that has lasted 6 months or more
Other indications	The member has another FDA-labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, American Hospital Formulary Service (AHFS), or National Comprehensive Cancer Network (NCCN) compendium recommended use 1 or 2a

Continuation of ritlecitinib (Litfulo) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for ritlecitinib has been previously approved by Florida Blue [Note: members not previously approved for the requested agent will require initial evaluation review]
2. Member has had clinical benefit with ritlecitinib therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist for alopecia areata) or the prescriber has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA-labeled contraindications to ritlecitinib
5. Member will **NOT** be using ritlecitinib in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a", "b", "c", or "d"):
    a. The dosage does not exceed 50 mg once daily
        - QL: 28 capsules/28 days (one per day)
    b. The member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
        ii. **ALL** of the following ("1", "2", and "3"):

4. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
5. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
6. **EITHER** of the following ("a" or "b"):
    a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
    b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

iii. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit

iv. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):

i. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Treatment of severe alopecia areata (AA) in adults and adolescents 12 years and older
    - Limitation of Use (per product labeling): Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.
    - The recommended dosage is 50 mg orally once daily with or without food. Swallow capsules whole. Do not crush, split, or chew capsules.

- Initiation is not recommended in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3 or a platelet count <100,000/mm^3. Initiation is not recommended in patients with hepatitis B or hepatitis C. Initiation is not recommended in patients with active TB. For patients with latent TB or those with a negative latent TB test who are at high risk for TB, start preventive therapy for latent TB prior to initiation of ritlecitinib.

Dose Adjustments

- Adverse effects: Treatment should be discontinued if platelet count is <50,000/mm^3. Treatment should be interrupted if ALC is <500/mm^3 and may be restarted once ALC return above this value. 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.
- Hepatic impairment: No dosage adjustment is recommended for mild or moderate hepatic impairment. Ritlecitinib has not been studied in patients with severe (Child Pugh C) hepatic impairment and is not recommended for use in these patients.
- Renal impairment: Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- 50 mg size 3, opaque capsules with a yellow body and blue cap in a bottle of 28 capsules

PRECAUTIONS:

Boxed Warning

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

- Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment if serious infection occurs until the infection is controlled. Litfulo should not be given to patients with active tuberculosis. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test.
- Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase inhibitor (JAK) vs. TNF blockers in rheumatoid arthritis (RA) patients. Litfulo is not approved for use in RA patients.
- Malignancies have occurred in patients treated with Litfulo. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients.
- Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients.
- Thrombosis has occurred in patients treated with Litfulo. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers.

Contraindications

- Patients with known hypersensitivity to ritlecitinib or any of its excipients

Precautions/Warnings

- **Serious Infections** - see Boxed Warning

- **Mortality** - see Boxed Warning
- **Malignancy and Lymphoproliferative Disorders** - see Boxed Warning
- **Major Adverse Cardiovascular Events** - See Boxed Warning
- **Thrombosis** - see Boxed Warning
- **Hypersensitivity** - Serious reactions including anaphylactic reactions, urticaria and rash have been observed in patients receiving ritlecitinib in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue and institute appropriate therapy
- **Laboratory Abnormalities** - Treatment with ritlecitinib was associated with decreases in lymphocytes and platelets. Prior to initiation, perform ALC and platelet counts. After initiating treatment, treatment interruption or discontinuation are recommended based on ALC and platelet count abnormalities. Treatment with ritlecitinib was associated with increased incidence of liver enzyme elevation compared to placebo. Increases of ALT ≥5 times the upper limit of normal (ULN) and increases of AST ≥5 times the ULN were observed in patients in ritlecitinib clinical trials. Evaluate 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 ritlecitinib until this diagnosis is excluded. Treatment with ritlecitinib was associated with increased incidence of CPK elevation compared to placebo.
- **Vaccinations** - No data are available on the response to vaccination in patients receiving ritlecitinib. Use of live attenuated vaccines should be avoided during or shortly prior to initiating treatment. Prior to initiating ritlecitinib, it is recommended that patients be brought up to date with all immunizations, including prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

L63.0 – L63.9	Alopecia areata

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

None

RELATED GUIDELINES:

Baricitinib (Olumiant), 09-J3000-10

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

REFERENCES:

1. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 10/29/24.
2. Ezzedine K, Peeva E, Yamaguchi Y, et al. Efficacy and safety of oral ritlecitinib for the treatment of active nonsegmental vitiligo: A randomized phase 2b clinical trial [published correction appears in J Am Acad Dermatol. 2023 Apr 6;:]. J Am Acad Dermatol. 2023;88(2):395-403.
3. Gilhar A, Etzioni A, Paus R. Alopecia areata. N Engl J Med. 2012 Apr 19;366(16):1515-25.
4. King B, Zhang X, Harcha WG, et al. Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomised, double-blind, multicentre, phase 2b-3 trial [published correction appears in Lancet. 2023 Jun 10;401(10392):1928]. Lancet. 2023;401(10387):1518-1529.
5. Litfulo (ritlecitinib capsule) [package insert]. New York, NY: Pfizer Inc., June 2023.
6. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 10/29/24.
7. Messenger AG, McKillop J, Farrant P, et al. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Br J Dermatol 2012; 166:916.
8. Peeva E, Guttman-Yassky E, Banerjee A, et al. Maintenance, withdrawal, and re-treatment with ritlecitinib and brepocitinib in patients with alopecia areata in a single-blind extension of a phase 2a randomized clinical trial. J Am Acad Dermatol. 2022;87(2):390-393.
9. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J Am Acad Dermatol. 2018 Jan;78(1):1-12.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/24.

GUIDELINE UPDATE INFORMATION:

10/01/23	New Medical Coverage Guideline.
01/01/24	Revision: New drugs were added to the list of drugs that are not permitted for use in combination.

07/01/24	Revision to guideline consisting of updating the position statement, and other section. Removal of latent TB testing requirement. New drugs added to the list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/25	Review and revision to guideline consisting of updating the position statement, other section, and references. Revised wording regarding dosage limit exceptions. New drugs added to the list of drugs that are not permitted for use in combination.