

Reimbursement Recommendation

Ritlecitinib (Litfulo)

Indication: For the treatment of adults and adolescents 12 years and older with severe alopecia areata

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Litfulo?

Canada's Drug Agency (CDA-AMC) recommends that Litfulo be reimbursed by public drug plans for "the treatment of adults and adolescents 12 years and older with severe alopecia areata" if certain conditions are met.

Why Did CDA-AMC Recommend Reimbursement?

Evidence from 1 clinical trial (ALLEGRO 2b/3) demonstrated that treatment with Litfulo improved hair regrowth of the scalp, eyebrows, and eyelashes compared with placebo in adults and adolescents aged 12 years and older with severe alopecia areata. In addition, an overall improvement was reported by a greater proportion of patients treated with Litfulo compared with placebo. However, there was little to no meaningful improvement in patient-reported symptoms of anxiety and depression for patients treated with Litfulo compared to placebo.

The Canadian Drug Expert Committee (CDEC) determined that Litfulo demonstrates acceptable clinical value versus placebo in adults and adolescents aged 12 years and older with severe alopecia areata. This determination was enough for CDEC to recommend that Litfulo be reimbursed. Given that Litfulo is expected to be an alternative treatment option to baricitinib, acceptable clinical value refers to at least comparable value versus baricitinib. Evidence from indirect treatment comparisons suggested that scalp hair regrowth outcomes were similar between Litfulo and baricitinib in adults with severe alopecia areata.

Litfulo may address an important unmet treatment need, particularly among adolescents with severe alopecia areata for whom targeted treatment options are limited.

Which Patients Are Eligible for Coverage?

Litfulo should only be covered for adults and adolescents aged 12 years and older with severe alopecia areata.

What Are the Conditions for Reimbursement?

Litfulo should only be reimbursed based on the criteria used by each of the public drug plans for initiation (with the exception of age), renewal, discontinuation, and prescribing of baricitinib and the cost of Litfulo does not exceed the total cost of treatment with the least costly JAK inhibitor reimbursed for the same indication.

Review Background

- **Disease background:** Alopecia areata is an autoimmune condition characterized by rapid, unpredictable nonscarring hair loss that can result in substantial emotional and psychosocial burden, including reduced self-confidence, shame, guilt, and impaired quality of life (QoL) for patients and caregivers. Alopecia areata can occur at any age, but most people (83% to 88%) develop the disease before 40 years of age, and approximately 70% of cases of alopecia areata occur between 10 and 25 years of age. Alopecia areata affects about 2% of the general population worldwide, with the prevalence in Canada estimated between 0.1% and 0.58%, of whom less than 5% are estimated to have severe disease.
- **Indication and reimbursement request:** Ritlecitinib has been approved by Health Canada for “the treatment of adults and adolescents 12 years and older with severe alopecia areata.” The sponsor is seeking reimbursement as per the Health Canada indication.
- **Drug under review:** Ritlecitinib is a member of the class of drugs called selective JAK3 and tyrosine kinase expressed in hepatocellular carcinoma family inhibitors. It is administered orally and the dosage recommended in the product monograph is 50 mg once daily.
- **Treatment costs:** At the submitted price of \$49.67 per capsule, the annual cost of ritlecitinib is expected to be \$18,142 per patient, based on the Health Canada–recommended dosage.

Highlights of Input From Interested Parties

The patient group (Canadian Alopecia Areata Foundation and Canadian Skin Patient Alliance) input noted the following regarding impacts of alopecia areata, unmet needs, and important outcomes:

- Patients with alopecia areata experience negative psychological, social, and functional impacts related to unpredictable hair loss including emotional distress, anxiety, and stigma. Caregivers often experience sadness, guilt, or helplessness related to the condition.
- The negative impacts of the disease were especially highlighted among adolescent patients, who reported experiences of being bullied by peers, social exclusion and missing school, or struggling academically due to emotional distress.
- Current treatments do not adequately address key unmet needs in alopecia areata, particularly the psychological and social impact, and the impacts of persistent or insufficient hair regrowth.
- The most important treatment goals for patients with alopecia areata are full and sustained hair regrowth and improved side effects associated with treatment while maintaining health-related quality of life (HRQoL).

No input was received from a clinician group. The clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from the disease and place in therapy for the drug under review:

- Currently available treatments for alopecia areata are limited by restricted access, variable treatment response, and safety concerns with existing systemic therapies.

- The clinical experts emphasized a substantial unmet need for effective treatment options for children and adolescents with severe alopecia areata, as baricitinib is currently indicated only for adult patients in Canada.
- Ritlecitinib should be considered as a first-line treatment option for severe alopecia areata.

The participating public drug programs raised potential implementation issues related to considerations for initiation, renewal, discontinuation, and prescribing of therapy.

Recommendation

With a vote of 15 in favour to 0 against, CDEC recommends that ritlecitinib be reimbursed for “the treatment of adults and adolescents 12 years and older with severe alopecia areata” only if the conditions listed in [Table 1](#) are met.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, and prescribing		
1. Ritlecitinib should be initiated in patients aged 12 years and older with severe alopecia areata. Additional reimbursement criteria for ritlecitinib should be based on the criteria used by each of the public drug plans for initiation (with the exception of age), renewal, discontinuation, and prescribing of baricitinib.	There is insufficient evidence to suggest that ritlecitinib should be held to a different standard than baricitinib for the treatment of patients with severe alopecia areata.	For jurisdictions that do not reimburse baricitinib, the additional initiation, renewal, and prescribing conditions for ritlecitinib should be consistent with the criteria recommended by CDEC for baricitinib for the treatment of severe alopecia areata.
Pricing		
2. The total cost of ritlecitinib should be negotiated so that it does not exceed the total cost of treatment with the least costly JAK inhibitor reimbursed for the same indication.	Based on the committee’s assessment of the evidence, ritlecitinib is expected to have broadly comparable benefits and harms compared with baricitinib. Therefore, the total cost of ritlecitinib should be no more than baricitinib.	—

CDEC = Canadian Drug Expert Committee.

Rationale for the Recommendation

Clinical Value

Based on the totality of the clinical evidence, CDEC concluded that ritlecitinib demonstrates acceptable clinical value compared with appropriate comparators for the treatment of severe alopecia areata in adults and adolescents aged 12 years and older. An appropriate comparator in the adult population refers to

baricitinib. Given that ritlecitinib is expected to be an alternative to baricitinib, acceptable clinical value refers to at least comparable value versus baricitinib.

Evidence from 1 phase 2b/3, randomized, double-blind, placebo-controlled study (ALLEGRO 2b/3) demonstrated that treatment with ritlecitinib for 24 weeks resulted in added clinical benefit for adults and adolescents aged 12 years and older with severe alopecia areata compared with placebo. Treatment with ritlecitinib for 24 weeks results in a clinically important increase in the proportion of patients achieving Severity of Alopecia Tool (SALT) score of 20 and likely results in a clinically important increase in the proportion of patients achieving SALT scores of 10 or less compared with placebo. In addition, ritlecitinib also likely results in a clinically important increase in the proportion of patients achieving improvement in eyebrow and eyelash hair regrowth outcomes (defined as at least a 2-grade improvement or a score of 3 in eyebrow assessment and eyelash assessment scores) compared with placebo. Ritlecitinib was generally well tolerated during the 24-week placebo-controlled period compared with placebo, and the safety profile was consistent with that of oral JAK inhibitors.

No head-to-head comparisons between ritlecitinib and relevant comparators were submitted. The sponsor submitted indirect comparative evidence comparing ritlecitinib versus baricitinib in adults with alopecia areata using network meta-analyses for randomized controlled trial data and matching adjusted indirect comparison analyses for longer-term data. Results suggest that the efficacy of ritlecitinib relative to baricitinib for scalp hair regrowth (SALT score ≤ 20 and SALT score ≤ 10) is similar at week 24 as there were no differences in the point estimates between treatments. CDEC concluded the efficacy of ritlecitinib is at least comparable to baricitinib, and therefore supportive of ritlecitinib as another treatment option for the treatment of patients with severe alopecia areata.

Further information on the committee's discussion around clinical value is provided in the Summary of Deliberation section.

Further information on the committee's discussion around unmet nonclinical need is provided in the Distinct Social and Ethical Considerations domain in the Summary of Deliberation section.

Developing the Recommendation

The determination of acceptable clinical value was sufficient for CDEC to recommend reimbursement of ritlecitinib. As part of the deliberation on whether to recommend reimbursement, the committee also considered unmet clinical need, unmet nonclinical need, and health inequity. Information on this discussion is provided in the Unmet Clinical Need and Distinct Social and Ethical Considerations domains in the Summary of Deliberation section.

Because CDEC recommended that ritlecitinib be reimbursed, the committee also deliberated on whether reimbursement conditions should be added to address important economic considerations, health system impacts, or social and ethical considerations, or to ensure clinical value is realized. The resulting reimbursement conditions, with accompanying reasons and implementation guidance, are stated in [Table 1](#).

Summary of Deliberation

CDEC considered all domains of value of the deliberative framework before developing its recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, refer to [Expert Committee Deliberation at Canada's Drug Agency](#).

The committee considered the following key discussion points, organized by the 5 domains of value.



Clinical Value

- **Appropriate comparators:** CDEC considered baricitinib to be the most relevant comparator for adults with severe alopecia areata in the treatment landscape in Canada. As baricitinib is not indicated for adolescents, placebo (best supportive care) was considered an appropriate comparator for this population; however, CDEC noted that other therapies such as corticosteroids, immunosuppressants, and other adjunctive treatments are commonly used in this population. Comparative evidence versus baricitinib was available only through indirect treatment comparisons in adult patients, and no direct or indirect comparative evidence was available versus other commonly used therapies in either adult or adolescent populations.
- **Efficacy versus baricitinib:** The sponsor-submitted indirect treatment comparisons evaluated the comparative efficacy of ritlecitinib versus baricitinib primarily for scalp hair regrowth at week 24, using placebo-anchored Bayesian network meta-analyses, with additional unanchored matching adjusted indirect comparison analyses for week 48 and week 52 time points. Evidence suggested that ritlecitinib and baricitinib had broadly similar treatment efficacy on scalp hair regrowth outcomes based on SALT scores of 20 and SALT scores of 10. The results showed no meaningful differences between ritlecitinib versus baricitinib for changes in anxiety or depression symptoms. CDEC noted that confidence in the comparative efficacy estimates was limited because of important differences between studies, sparse evidence networks, wide credible intervals, and methodological limitations associated with the long-term indirect comparisons. Beyond week 24, comparative analyses relied on unanchored matching adjusted indirect comparison methods due to the absence of a connected placebo network, leading to greater uncertainty in the longer-term comparative estimates.
- **Efficacy versus placebo:** Evidence from the ALLEGRO 2b/3 study (N = 261) showed that a greater proportion of patients treated with ritlecitinib achieved clinically meaningful scalp hair regrowth at 24 weeks compared with placebo, as measured by the proportion of patients with SALT scores of 20 (23.4% versus 1.5%) and SALT scores of 10 (13.4% versus 1.5%). A greater proportion of patients treated with ritlecitinib also experienced a clinically meaningful improvement in eyebrow hair regrowth (29% versus 4.6%) and eyelash hair regrowth (29% versus 5.2%) compared with placebo. Compared with placebo, a greater proportion of patients treated with ritlecitinib reported an overall improvement (49.6% versus 5.1%). In contrast, ritlecitinib resulted in little to no clinically important difference in anxiety and depression when compared with placebo. No new safety signals were reported during the 24-week placebo-controlled period. CDEC noted that the ALLEGRO 2b/3 study evaluated the

efficacy and safety of ritlecitinib versus placebo over a 24-week placebo-controlled period, resulting in limited comparative evidence on long-term outcomes. To address this limitation, the sponsor submitted evidence from the ongoing ALLEGRO-LT open-label extension study (N = 449), which suggested that scalp, eyebrow, and eyelash hair regrowth outcomes may be maintained or improve with continued treatment for up to 36 months. However, CDEC concluded that the certainty of the long-term extension data compared to any comparator was very low because of the noncomparative study design and the potential for selection and attrition bias.

- **Impact of treatment on anxiety and depression:** The committee acknowledged the significant impact of alopecia areata on mental health, including anxiety and depression. However, improvements in hair regrowth with ritlecitinib were not accompanied by corresponding improvements in these outcomes in the ALLEGRO 2b/3 study. The clinical experts suggested that this may be due to the relatively short duration of the studies that were likely insufficient to capture downstream psychosocial benefits, which are expected to be observed with continued improvement of hair regrowth over a few years. Additionally, variability in disease presentation, including the location and extent of hair loss, may influence the extent to which hair regrowth translates into measurable improvements in mental health within the study time frame.
- **Clinical importance of treatment effects:** CDEC considered the treatment effects observed with ritlecitinib to be clinically meaningful given that scalp, eyebrow, and eyelash hair regrowth outcomes were identified by patients and clinical experts as important treatment goals. CDEC also noted that patient-reported improvements in the overall efficacy of a treatment measured using the Patient Global Impression of Change supported meaningful improvement in patients' overall perception of their disease status. CDEC also noted that ritlecitinib may address an unmet treatment need, particularly among adolescents with severe alopecia areata for whom targeted treatment options are limited.
- **Certainty of the evidence:** CDEC concluded that the evidence supporting a clinically meaningful improvement in scalp hair regrowth based on SALT scores of 20 at week 24 was of high certainty. The evidence for SALT score of 10 was assessed to be of moderate certainty due to imprecision in the effect estimate, as the 95% confidence interval crossed the target threshold and included effects ranging from little or no important difference to clinically important benefit. The evidence for eyebrow and eyelash hair regrowth outcomes was also assessed to be of moderate certainty because these outcomes were evaluated only among patients with baseline eyebrow or eyelash involvement and were not adjusted for multiplicity. The evidence for patient-reported improvements in the overall efficacy of a treatment measured using the Patient Global Impression of Change was of high certainty and supported a clinically meaningful treatment effect. In contrast, CDEC noted little to no clinically important difference between ritlecitinib and placebo for anxiety and depression outcomes. The certainty of evidence for serious adverse events was low because of very low event rates and substantial imprecision in the effect estimates.
- **Criteria for initiation and renewal of therapy:** CDEC discussed that, although achievement and maintenance of SALT score of 20 is considered as a clinically meaningful treatment response

for renewal of therapy, some patients with severe disease at baseline may experience clinically meaningful benefit without achieving this threshold. The clinical experts noted that a 50% improvement from baseline in SALT scores may also represent meaningful improvement in some patients, particularly among those with extensive hair loss at baseline (i.e., a higher SALT score at baseline). The clinical experts also indicated that the site of the hair loss, such as the eyebrows or eyelashes, is another meaningful way of identifying patients with severe alopecia areata. However, CDEC noted there is no evidence to support the use of eyebrow and eyelash hair regrowth outcomes as an alternative to SALT-based measures for initiation or renewal criteria.

- **Clinical value:** Based on the totality of the evidence, CDEC concluded that ritlecitinib demonstrated acceptable clinical value for patients with severe alopecia areata, particularly in improving scalp, eyebrow, and eyelash hair regrowth outcomes. CDEC further concluded that ritlecitinib may provide similar clinical benefit relative to baricitinib in adults, although comparative evidence remains uncertain.



Unmet Clinical Need

- **Input on unmet clinical need:** Patient group input highlighted the need for effective treatments that provide substantial and sustained hair regrowth with manageable side effects for patients with severe alopecia areata. Patients noted limitations of existing therapies, including topical and intralesional corticosteroids, off-label systemic immunosuppressants, and other supportive approaches, citing limited efficacy, treatment burden, and safety concerns. Patients and clinicians also highlighted the lack of targeted treatment options for adolescents. Patients further expressed a need for treatments that improve QoL.
- **Severity of the disease:** CDEC recognized that the visible hair loss associated with severe alopecia areata can substantially impair QoL, self-image, and daily functioning. In addition to scalp hair loss, CDEC acknowledged that eyebrow and eyelash hair loss may have functional consequences because eyebrows and eyelashes serve a protective function by preventing foreign substances from entering the eyes. Patient and clinician input indicated that the burden of disease may be particularly pronounced among adolescents, in whom visible hair loss can negatively affect social development and school experiences.
- **Availability of treatment options:** CDEC noted that currently available treatments for severe alopecia areata include topical and intralesional corticosteroids, off-label conventional systemic immunosuppressants, and JAK inhibitors. According to the clinical experts consulted for this review, topical and intralesional therapies are generally not effective for the treatment of severe disease, while conventional systemic therapies are associated with limited efficacy and important safety concerns. CDEC noted that baricitinib was considered a relevant treatment option for adults with severe alopecia areata, but it is not indicated for children or adolescents. As such, CDEC noted that targeted treatment options for adolescents with severe alopecia areata remain limited.



Distinct Social and Ethical Considerations

- **Input on unmet nonclinical need:** CDEC acknowledged significant unmet nonclinical needs associated with severe alopecia areata, related to, social and functional well-being of visible hair loss. Patient group input highlighted stigma, social withdrawal, impaired self-esteem, bullying, school-related challenges, and avoidance of social activities, particularly among adolescents. Patients and caregivers also described financial burden associated with wigs, cosmetic adaptations, and lack of public reimbursement for treatments. According to the clinical experts, wigs and other cosmetic adaptations may not adequately address the impact of alopecia areata because they can be impractical or uncomfortable during activities such as swimming, sports, and exercise, resulting in additional limitations on participation in daily activities.
- **Equity considerations:** CDEC acknowledged equity considerations related to limited access to dermatology specialists and effective treatments for patients living in rural, remote, and underserved communities, as well as the disproportionate psychosocial burden experienced by adolescents with severe alopecia areata.



Economic Considerations

- **Health impacts of ritlecitinib versus relevant comparators:** Evidence submitted by the sponsor indicates that ritlecitinib is likely to increase the proportion of patients achieving improvement in scalp hair regrowth compared with placebo among patients with severe alopecia areata. According to the Clinical Review report, results from the sponsor-submitted indirect treatment comparison (ITC) suggest broadly similar efficacy for scalp hair regrowth outcomes at week 24. However, definitive conclusions were limited by wide credible intervals and methodological limitations in the ITC. Comparative evidence for patient-reported outcomes and safety was also uncertain. As such, there is uncertainty whether ritlecitinib has similar clinical efficacy to baricitinib, and uncertainty in the efficacy estimates between the treatments was not incorporated in the sponsor's economic analysis.
- **Cost of ritlecitinib versus relevant comparators:** If there are no differences in health outcomes between ritlecitinib and baricitinib, then the impact of ritlecitinib on costs will depend solely on drug acquisition costs.
- **Key findings of the economic evaluation:** The cost-effectiveness of ritlecitinib compared with baricitinib is uncertain. Based on the CDA-AMC clinical review of the sponsor-submitted ITC, the comparative efficacy in terms of scalp hair regrowth of ritlecitinib relative to baricitinib may be broadly similar. If there are no differences in health outcomes between ritlecitinib and baricitinib, then the total cost of ritlecitinib to health systems should not exceed that of baricitinib for the treatment of alopecia areata. Baricitinib is not available for adolescents (patients aged 12 to 17 years) in Canada. Cost-effectiveness could not be determined in this population due to limitations with the sponsor's submitted analysis.
- **Certainty of the evidence:** In the comparison with baricitinib, results from the sponsor-submitted ITC are uncertain due to several limitations including imprecision, cross trial heterogeneity, and

methodological limitations. Results for safety and patient-reported anxiety and depression were uncertain. In the comparison with best supportive care, CDA-AMC identified numerous key issues with the sponsor's submitted analysis, not all of which could be resolved by CDA-AMC. The result was that the sponsor's analysis was uninformative for decision-making. Key remaining areas of uncertainty include the long-term efficacy of ritlecitinib compared with placebo and the impact of ritlecitinib on HRQoL.



Impacts on Health Systems

- **Anticipated budget impact:** CDA-AMC estimated the budget impact of reimbursing ritlecitinib for the treatment of severe alopecia areata will be a savings of approximately \$11 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$85 million on ritlecitinib over this period. The actual budget impact of reimbursing ritlecitinib will depend on the eligible patient population size, the market uptake of ritlecitinib, and the displacement of the comparators, all of which are uncertain.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information (links to the full documents for the review can be found on the [project webpage](#)):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence submitted by the sponsor, as well as relevant ethical issues related to ritlecitinib (refer to the main report and Supplemental Material document)
- the sponsor's comments on the draft report and the CDA-AMC responses
- patients' perspectives gathered by 1 patient group, Canadian Alopecia Areata Foundation and Canadian Skin Patient Alliance (refer to the Patient and Clinician Group Input document)
- input from public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical experts with expertise in the management of alopecia areata consulted by CDA-AMC.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed.

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Regrets: None

Conflicts of interest: None



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