Litfulo Label Strengthened With New Alopecia Areata Safety Warnings

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Alopecia areata, an autoimmune condition causing patchy or complete hair loss, presents a significant quality of life burden for affected individuals. While several treatments exist, including corticosteroids and JAK inhibitors, the safety profile of newer agents remains a critical consideration for prescribers. The European Medicines Agency (EMA) recently strengthened warnings for Litfulo (ritlecitinib), a Janus kinase (JAK) 3 and TEC family kinase inhibitor, used for severe alopecia areata.

KEY TAKEAWAYS

- The Pivot: The EMA has updated Litfulo's product information to include new safety warnings, aligning it more closely with other JAK inhibitors.
- The Data: The warnings encompass risks of serious infections, major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, and mortality.
- The Action: Clinicians should re-evaluate patient risk factors for these serious events before initiating or continuing Litfulo, particularly in older patients or those with comorbidities.

Alopecia areata affects approximately 1% to 2% of the general population, with severe forms leading to total scalp hair loss (alopecia totalis) or total body hair loss (alopecia universalis).1 The condition's unpredictable course and visible nature often result in considerable psychological distress, including anxiety and depression, underscoring the need for effective and safe treatments. Before the advent of JAK inhibitors, treatment options were largely limited to topical or intralesional corticosteroids, contact immunotherapy, or systemic immunosuppressants, all with varying efficacy and significant side effect profiles.1

Litfulo, developed by Pfizer, received EMA approval in August 2023 for the treatment of severe alopecia areata in adults and adolescents 12 years and older.2 Its mechanism of action involves inhibiting JAK3 and the TEC family kinases, which are involved in the signalling pathways that contribute to the autoimmune attack on hair follicles. This targeted approach aims to modulate the immune response responsible for hair loss. The approval was primarily based on data from the ALLEGRO Phase 2b/3 trial program, which evaluated the efficacy and safety of ritlecitinib in a diverse patient population.3

The new safety landscape

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of JAK inhibitors in 2022, following concerns raised by the ORAL Surveillance study for tofacitinib in rheumatoid arthritis.4 That study, which compared tofacitinib with TNF inhibitors, identified increased risks of MACE, VTE, malignancy, and serious infections.

While Litfulo is a selective JAK3 inhibitor and not directly comparable to tofacitinib, the class-wide review prompted a re-evaluation of all JAK inhibitors, including those approved for dermatological conditions. The EMA concluded that these risks are class effects, necessitating updated warnings across the board.4

The updated product information for Litfulo now explicitly warns of increased risks for several serious adverse events. These include serious infections, such as pneumonia, herpes zoster, and tuberculosis, which can lead to hospitalisation or death. Clinicians must screen patients for active and latent infections before initiating therapy and monitor them closely during treatment. The risk of major adverse cardiovascular events (MACE), including myocardial infarction and stroke, also received a strengthened warning. This risk appears elevated in patients with existing cardiovascular risk factors, particularly older patients and smokers.4

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, is another critical safety concern. The EMA advises caution in patients with known VTE risk factors, such as a history of VTE, obesity, or prolonged immobilisation. Malignancies, including non-melanoma skin cancer and lymphoma, have also been associated with JAK inhibitor use. Regular skin examinations are recommended, especially for patients with increased risk factors for skin cancer. Finally, the updated label includes a warning regarding overall mortality, particularly in older patients and those with multiple comorbidities.4

These warnings are not unique to Litfulo but reflect a broader understanding of the JAK inhibitor class. Tofacitinib (Xeljanz), baricitinib (Olumiant), and upadacitinib (Rinvoq), all approved for various autoimmune conditions, carry similar warnings. The PRAC's review highlighted that these risks are generally higher in patients aged 65 years and older, current or past smokers, and those with other cardiovascular risk factors or malignancy risk factors.4 This necessitates a careful individual risk-benefit assessment before prescribing Litfulo, especially for patients in these higher-risk categories.

The ALLEGRO trials, which supported Litfulo's approval, did report adverse events consistent with the JAK inhibitor class. In the ALLEGRO-2b/3 trial, the most common adverse events (≥5%) included headache, nasopharyngitis, and upper respiratory tract infection.3 Serious adverse events, while less frequent, included infections and creatine phosphokinase elevations. The trial enrolled 718 patients, randomising them to ritlecitinib 50 mg, 30 mg, 10 mg, or placebo. At week 24, 23% of patients receiving ritlecitinib 50 mg achieved 90% or more scalp hair coverage (SALT score ≤10), compared to 1.6% in the placebo group (difference 21.4 percentage points; 95% CI, 16.5-26.2; P<.0001).3 This efficacy must now be weighed against the more clearly defined and strengthened safety profile. The trial was not powered to detect differences in rare serious adverse events, which is a common limitation in pre-market studies for drugs in this class. Long-term safety data, often gathered post-marketing, are crucial for a complete understanding of these risks.

The EMA's decision to strengthen these warnings underscores a cautious approach to new therapies, particularly those with systemic immune modulation. It reinforces the need for clinicians to engage in thorough patient counselling, ensuring individuals understand the potential benefits of hair regrowth against the backdrop of serious, albeit rare, systemic risks. The prescribing information now explicitly advises against initiating Litfulo in patients with active serious infections and recommends interruption of treatment if a serious infection develops.4

CLINICAL IMPLICATIONS

> The EMA's updated warnings for Litfulo are not merely administrative changes; they demand a tangible shift in clinical practice for European GPs and specialists. Prescribers must now conduct a more rigorous pre-treatment assessment, particularly for patients over 65, smokers, or those with a history of cardiovascular events or malignancy. This is not a suggestion; it is a directive to protect vulnerable patients.
> The class-wide nature of these JAK inhibitor warnings means that clinicians cannot assume a newer, more selective agent like Litfulo is exempt from the risks identified with older drugs like tofacitinib. The onus is on the prescriber to understand the nuanced risk profile of each patient and to communicate these risks transparently. Simply put, if a patient has significant cardiovascular risk factors, the benefit of hair regrowth must be weighed against a potentially increased risk of MACE.
> For patients, these warnings introduce a new layer of complexity to treatment decisions. While the desire for hair regrowth is often profound, the prospect of serious infections, VTE, or cardiovascular events may temper enthusiasm. Clinicians must facilitate informed consent that genuinely reflects these updated risks, ensuring patients understand the trade-offs involved with long-term systemic therapy.
> Pfizer, like other manufacturers of JAK inhibitors, now faces the challenge of navigating a more stringent regulatory environment. The market for alopecia areata treatments is expanding, but the heightened scrutiny on safety means that future drug development and post-marketing surveillance will need to be exceptionally robust. The era of assuming a new mechanism equates to a cleaner safety profile is clearly over.

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