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Review Article

Litfulo : Is An Innovative Medication

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ABSTRACT

Alopecia areata is an autoimmune disorder characterized by transient, non-scarring hair loss and preservation of the hair follicle. Hair loss can take many forms ranging from loss in well-defined pat\ches to diffuse or total hair loss, which can affect all hair-bearing sites.Pfizer is developing ritlecitinib (LITFULOTM), an oral kinase inhibitor, to treat Crohn's disease, vitiligo, alopecia areata, and ulcerative colitis. Ritlecitinib was approved in the United States on June 23, 2023, for the treatment of severe alopecia areata in adults and adolescents aged 12 and above. On June 26, 2023, ritlecitinib received approval in Japan to treat alopecia areata, a condition limited to incurable cases resulting in extensive hair loss. Ritlecitinib is undergoing regulatory reviews in China and the UK and has also been given a positive opinion in the EU. The key developments in ritlecitinib's development that led to its initial approval for the treatment of severe alopecia areata are outlined in this article.

INTRODUCTION

Pfizer is developing ritlecitinib (LITFULOTM), a kinase inhibitor, to treat Crohn's disease, vitiligo, alopecia areata, and ulcerative colitis. Janus kinase 3 (JAK3) and the tyrosine kinase expressed in the TEC kinase family of hepatocellular carcinoma (TEC) are irreversibly inhibited by ritlecitinib [1].Ritlecitinib was first approved in the United States on June 23, 2023, for the treatment of severe alopecia areata in adults and adolescents aged 12 and up. In the United States, 6.7 million people suffer with alopecia. [1, 2]. An autoimmune condition called alopecia areata is characterized by hair loss on the scalp,face,and/or body [2]. It is not advised to use ritlecitinib in conjunction with ciclosporin, biologic immunomodulators, other strong immunosuppressants, or other JAK inhibitors [1]. 50 mg of ritlecitinib taken once daily, with or without food, is the recommended dosage.On June 26, 2023, it received approval in Japan for the treatment of alopecia areata, with the exception of severe cases involving extensive hair loss [3]. On July 20, 2023, the EU gave ritlecitinib a positive opinion for the treatment of alopecia

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areata [4]. Ritlecitinib is the pioneer drug in a novel class of crosslinking kinase inhibitors that has excellent janus kinase 3 (JAK3) selectivity. Ritlecitinib has been demonstrated in laboratory studies to block the activity of immune cells and signaling molecules that result in chronic hair loss in alopecia patients. A JAK3 inhibitor that is irreversible, ritlecitinib, was also reported. These inhibitors' chemical structures contain covalent bonds that create groups like acrylamide and alpha cyanoacrylamide that can attach to the Cys909 residue. Alopecia areata is a disease where the body's own immune system attacks hair follicles, causing inflammation that leads to hair loss on the scalp, face and/or other parts of the body. Impacting approximately 2 percent of the population at some point during their lifetime, alopecia areata can affect people of any age, gender, race, or ethnicity and can cause considerable burden beyond hair loss [5].

Drug summary :

Generic Name: ritlecitinib capsules

Brand Name: Litfulo

Drug Class: Dermatologics, Other, Antineoplastic Tyrosine Kinase Inhibitors

What is Litfulo ?

Litfulo (ritlecitinib) is a kinase inhibitor indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older.

Pharmacodynamic:

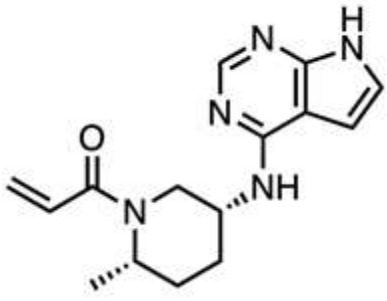
Ritlecitinib's selective dual inhibition of JAK3 and TEC kinase family members may prevent the signalling of different cytokines and T cell cytolytic activity, which is linked to the ethology of inflammatory and autoimmune disorders [6].Becau se ritlecitinib binds irreversibly to a cysteine residue at position 909 (Cys-909) in JAK3, which is substituted with a serine residue at the same position in other JAK isoforms, ritlecitinib inhibits JAK3 with a high degree of selectivity over other JAK isoforms [6]. With a half maximal inhibitory concentration (IC50) of 33.1 nM, ritlecitinib inhibits JAK3 in vitro . Ritlecitinib exhibits a lower affinity (IC50 > 10,000 nM) for tyrosine kinase 2 (TYK2), JAK1, and JAK2 [6]. Pharmacokinetics: Up to 200 mg, the maximum plasma concentration (Cmax) increases roughly dose proportionately, reaching steady state after 4 days [1]. Cmax is attained an hour after an oral dose. Food does not appear to have a clinically significant impact on ritlecitinib exposure, as demonstrated by the 11% increase in AUC∞ and 32% decrease in Cmax following the administration of 100 mg of ritlecitinib .Ritlecitinib has an absolute oral bioavailability of ≈64%, and only 14% of the drug in circulation is bound to plasma proteins. When ritlecitinib and CYP1A2 and CYP3A substrates are administered together, there is a chance that this will expose these substrates more, which raises the possibility of negative reactions [1, 7]. Several pathways are involved in the metabolism of rilecitinib, including those involving cytochrome P450 (CYP) enzymes, specifically CYP1A2, CYP2C8, and CYP2C9, and glutathione S-transferase (GST), specifically GST A1/3, M1/3/5, P1, S1, T2, Z1, and microsomal GST 1/2/3.

MECHANISM OF ACTION

Litfulo is a kinase inhibitor: An autoimmune condition called alopecia areata results in hair loss, primarily on the hair follicles yet additionally on the skin of the face and various places. Follicles that produce hair are immune privileged areas that frequently have been defined by the presence of naturally subdued natural killer cells. Disruptions to this mechanism, however, can result in alopecia areata and the loss of immunological privilege.

Genome-wide association studies have connected the pathophysiology of alopecia areata to the amplification of UL16-binding protein 3 (ULBP3), a protein which binds to naturally occurring killer cell receptors. The attack of deadly clusters of differentiating 8-positive NK group 2D-positive is encouraged by the overexpression of ULBP3.One kinase inhibitor biis litfulo: Alopecia areata is an autoimmune disease that causes hair loss, mostly on the hair follicles but also on the skin around the face and in other areas. Hair-producing folicles are immune-privileged regions that are often characterized by naturally suppressed natural killer cells. However, interference with this mechanism can lead to immunological privilege loss and alopecia areata. Alopecia areata's pathophysiology has been linked by genome-wide association studies to the amplification of UL16-binding protein 3 (ULBP3), a protein that binds to naturally occurring killer cell receptors. The overexpression of ULBP3 promotes the attack of lethal clusters of differentiating 8-positive NK group 2D- positive. cells attacking hair follicles result in hair follicle dystrophy. CD8+ (NKG2D+) T cells stimulate the allergic response of hair follicles through the interferon alpha and interleukin 15signaling pathways. This activates the Janus Kinase (JAK)/signal transduction and promoter of transcription (STAT) biochemical pathways. Thus, JAK inhibitors have been proposed as a potential alopecia areata treatment. [8-9]Ritlecitinib irreversibly inhibits Janus Kinase 3 (JAK3) and the tyrosine kinase family expressed in hepatocellular carcinoma (TEC) kinase by blocking the adenosine triphosphate (ATP) binding site. In cellular settings, ritlecitinib inhibits the phosphorylation of STAT triggered by cytokinese accomplished by JAK3-dependent receptors , issues with the immune and cancer

LITFULO may increase your risk of getting some cancers by changing how your body's immune system operates. It is possible to develop skin cancers as well as other cancers like lymphoma. Individuals who take a JAK inhibitor, Smokers, whether they are current or past smokers, are more likely to develop certain cancers, like lung cancer and lymphoma. As instructed by your healthcare provider, examine your skin for signs of skin cancer while undergoing therapy. Inform your doctor if you or a loved one has ever experienced any type of cancer. Individuals who use a JAK inhibitor and are 50 years of age or older and susceptible to at least one cardiovascular risk factor are more likely to experience serious cardiovascular event.[10]



Structure of Ritlecitinib

Clinical Trials:

Areata alopecia ALLEGRO-2b/3 An international phase 2b/3 trial (NCT03732807; ALLEGRO-2b/3) that was randomized, double-blind, and treated alopecia areata showed efficacy with ritlecitinib [16].With a maximum duration of current episode of hair loss of ≤ 10 years, this trial included adults aged ≥ 18 years and adolescents aged 12–17 years with alopecia areata and ≥ 50% scalp hair loss (including alopecia totalis and alopecia universalis), as measured by the Severity of Alopecia Tool [SALT; scores range from 0 (no scalp hair loss) to 100 (total scalp hair loss). Other causes of alopecia and prior use of any JAK inhibitor were important exclusion criteria. Patients were randomly assigned to receive 50 mg (n = 132), 200 mg of ritlecitinib for four weeks after that, or 200 mg of ritlecitinib for four weeks after that.,[18]ALLEGRO-LT), ritlecitinib

demonstrated sustained clinical efficacy in patients with alopecia areata over the long term [10]. Rollover patients from ALLEGRO-2a and ALLEGRO-2b/3 as well as de novo patients who had not received treatment in prior ALLEGRO trials were enrolled in ALLEGRO-LT. Aged 12 years or older, they had alopecia areata-related scalp hair loss of at least 25%, no signs of terminal hair regrowth within 6 months, and a maximum duration of 10 years for the current hair loss episode. For four weeks, each patient received 200 mg of ritlecitinib once daily; after that, they were given 50 mg once daily (18).

Get emergency help right away if you have any symptoms of a heart attack or stroke while taking LITFULO, including: [11]

- Chest discomfort that continues for for in excess of a few minutes or that disappears then reappears
- Extreme chest, throat, neck, or tongue tenseness, pain, pressure, or stiffness
- Chest discomfort or shortness of breath, either alone or in combination with pain in the legs, back, neck, teeth.
- Sweating profusely; feeling queasy or sick; feeling dizzy; having weakness in one side or area of your body
- Severe pain, pressure, stiffness, or tenseness in the tongue, throat, chest, or neck
- Pain in the legs, back, neck, teeth, or stomach, either by itself or in conjunction with shortness of breath or discomfort in the chest
- Excessive perspiration; nausea or vomiting; vertigo; weakness in one side or part of the body; slurred speech

Significance:

Adolescents with severe alopecia areata 12 years of age and older are treated with a kinase inhibitor called LITFULO

Storage

Store at 20°C to 25°C (68°F to 77°F). Keep in original package.

Restrictions of Use:

It is not recommended to combine additional JAK inhibitors with biological immunomodulators, cyclosporine, or other potent immunosuppressants.

Children: The safety of Litfulo in children under 12 years of age has not been established.

Warnings

Litfulo is associated with an increased risk of serious bacterial, fungal, viral, and opportunistic infections that may lead to hospitalization or death, including tuberculosis (TB). Litfulo should not be started in those with active TB or a serious infection. Investigations for latent TB should be undertaken before and during therapy and treatment started and the infection cleared before starting Litfulo. All patients should be monitored for signs and symptoms of infection, including TB, during and after treatment.

Treatment of overdose:

In clinical trials, up to 800 mg of LITFULO was given orally in one dose. No specific adverse reactions were found, but they were equivalent to those encountered at lower doses. In healthy adult volunteers, pharmacokinetic data up towards and including an individual oral administration of 800 mg show that over ninety per cent of the dose that was given is anticipated to be eliminated within 48 hours. A specific LITFULO overdose remedy is not available. The patient should be monitored for signs and symptoms of an adverse response while receiving symptomatic and supportive treatment. During clinical trials, oral doses of up to 800 mg of LITFULO were administered. While no particular negative effects were observed, the ones that were experienced were comparable to those at lower dosages. Pharmacokinetic data up to and including an individual oral dosage of 800 mg in healthy adult volunteers demonstrate that more than 90% of the It is expected that the administered dose will be removed in 48 hours. There is currently no known treatment for LITFULO

overdose. It is important to keep an eye out for the patient's symptoms. having a negative reaction while undergoing supportive and symptomatic care. Patients need to inform to physician as soon as possible if you are suffering from an infection, receive medical care for one, or exhibit symptoms of one, such as:

- Fever, sweating, or chills
- Muscle aches
- Cough or shortness of breath Blood in your phlegm Weight loss Warm, red, or painful skin or sores on your body Diarrhoea or stomach pain Burning when you urinate or urinating more
- Often than usual Feeling very tired

Contraindications:

Severe side effects have been reported by LITFULO users in clinical trials, including rash, urticaria, and anaphylactic reactions. People who have previously experienced hypersensitivity to ritlecitinib or any of its excipients should not use LITFULO. If there is a hypersensitive reaction that is clinically significant, stop taking LITFULO and begin the appropriate treatment.

Side effects

The most common side effects are:

- Headache.
- Rashes
- Urticaria.
- Diarrhoea
- Acne.
- Atopic dermatitis
- Folliculitis
- Fever
- Dizziness
- Increases in laboratory values of creatine phosphokinase and decreases in red blood cell counts
- Mouth ulcers.

Interaction

1. Abatacept- The likelihood or intensity of side effects may escalate when combined with ritlecitinib.
2. Abemaciclib - Abemaciclib's serum levels can be increased when used in conjunction with ritlecitinib.
3. Abiraterone-The serum levels of abiraterone can be increased when combined with ritlecitinib.
4. Acyclovir-The serum levels of acyclovir can be increased when combined with ritlecitinib.
5. Rifampicin may lower ritlecitinib's AUC and Cmax, which may result in a loss or reduction of clinical response.
6. Rifampin will lessen the amount or effect of ritlecitinib by reducing the metabolism of the hepatic/intestinal enzyme CYP3A4.[12

Adverse action:

Areata Alopecia Based on an integrated safety analysis of data from ALLEGRO-2a, ALLEGRO-2a safety study, ALLEGRO-2b/3, and ALLEGRO-LT, ritlecitinib was well tolerated in alopecia areata patients [14]. Two cohorts were examined: an all-exposure pool comprising patients who received at least one dose of ritlecitinib in any of the four trials (n = 1294; 2092 total patient- years (PY) of exposure) and a placebo-controlled cohort from three trials (n = 881). The majority of adverse events (AEs) were self-limiting, of mild severity, and did not necessitate changing dosages or stopping treatment entirely. Ritlecitinib 50 mg once daily (the recommended dosage) was administered to 345 patients in the placebo-controlled cohort for a maximum of 24 weeks. Nasopharyngitis was one of the AEs that occurred in at least 10% of these patients and at a higher rate than the placebo.A cohort of adolescents from ALLEGRO-2b/3's 24-week placebo- controlled period (n = 105) and an any-ritlecitinib cohort of adolescents from ALLEGRO-2b/3 and/or ALLEGRO-LT who

received at least one dose of ritlecitinib (n = 181) provided the data. AEs happened in 67– 83% of ritlecitinib recipients and 79% of placebo recipients in the placebo- controlled cohort. Due to severe adverse events (AEs) including eczema and suicidal thoughts, two patients stopped taking ritlecitinib. The incidence of adverse events (AEs) in the any- ritlecitinib cohort was 83% (160.6/100 PY), with 4% (2.3/100 PY) of serious AEs. Acne (13.7/100 PY) and headache (13.3/100 PY) were the most common adverse events. [15]

Patent :

LITFULO (Ritlecitinib) capsule inventor: Lauren E. Ingram; Reference ID:5196496; Starting process approved-NDA 215830; Approved by: Federal Food Drug and Cosmetic Act.

Inventors:

BROWN, Mathew Frank, Massachusetts, CHE, Ye, COE-Jotham Wadsworth, FLANGAN, Mark Edward, GILBERT, Adam Matthew, HAYWARD, Matthew Merrill, LANGILLE, Jonathan David, MONTGOMERY, Justin Ian, TELLIEZ, Jean-Baptiste, THORARENSEN, Atli, UNWALLA, Rayomand Jal.

CONCLUSION:

The expression of TH1 markers was positively correlated with ritlecitinib rise in SALT scores;however, there was an inverse relationship between the total number of hair keratin proteins. Longer and more comprehensive clinical trials are needed. It worked well, was well tolerated, and may provide an option for people with alopecia areata who are old enough to obtain systemic treatment

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