A DIFFERENT WAY TO TREAT FAMILIAL MEDITERRANEAN FEVER

Learn about the clinical efficacy and safety of ILARIS in patients with FMF with active disease despite colchicine therapy or intolerance to effective doses of colchicine[1]

FMF, familial Mediterranean fever.

INDICATIONS

ILARIS® (canakinumab) is an interleukin-1β blocker indicated for the treatment of the following autoinflammatory Periodic Fever Syndromes:

- Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and pediatric patients 4 years of age and older, including:
  - Familial Cold Autoinflammatory Syndrome (FCAS)
  - Muckle-Wells Syndrome (MWS)
- Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients
- Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients
- Familial Mediterranean Fever (FMF) in adult and pediatric patients

ILARIS is indicated for the treatment of active Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years of age and older.

ILARIS is indicated for the symptomatic treatment of adult patients with gout flares in whom nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

IMPORTANT SAFETY INFORMATION

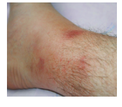
CONTRAINDICATIONS

ILARIS is contraindicated in patients with confirmed hypersensitivity to canakinumab or to any of the excipients.

Please see additional Important Safety Information throughout and full Prescribing Information, including Medication Guide, for ILARIS.

ILARIS® (canakinumab)
150 mg subcutaneous injection

FMF disease characteristics[2-8]

Predominant ethnic distribution	Turkish, Armenian, Arab, Jewish, Italian
Worldwide prevalence or number of cases	1 to 5 in 10,000
Typical age at onset	<20 years
Duration of attacks	12 hours to 3 days
Frequency of attacks	Irregular; once per week to once every 5 to 10 years
Gene mutation	MEFV
Inheritance	Autosomal recessive
Cutaneous findings	• Erysipelas-like erythema • Characterized by red, warm, and swollen areas • Lesions are tender to the touch, can be 10 cm to 15 cm in diameter, and usually occur below the knee on the anterior leg or top of foot 
Other select clinical features	• Abdominal pain • Chest pain • Arthritis/monoarthritis
High serology	Increase in CRP, ESR, and SAA

Rash image credit: Reproduced with permission from Emedmd.com.

Is a biologic appropriate for this patient?

26-year-old female of Middle Eastern descent with active FMF

Not an actual patient.

Patient presentation

- Intermittent fever, abdominal pain, and chest pain
- Weight=54 kg
- Reported to emergency room 4 times within the past year
- Intolerant to colchicine with frequent GI-related side effects

Patient medical history

- History of intermittent fever, abdominal pain, and chest pain
- Recurrent symptomatic flares occurring every 2 weeks, and lasting 2 to 3 days
- Patient complains of occasional headaches that occur unrelated to disease flares
- Past medical history otherwise unremarkable

Relevant family history

- Parents both healthy
- Maternal uncle with FMF diagnosis

Clinical and laboratory results

- Lab results (during an episode):
  - WBC: 14.7 x 10^9 cells/L
  - ESR: 58 mm/h
  - CRP: 19 mg/dL
  - Urinalysis: negative for proteinuria and hematuria
- Genetic testing results:
  - Compound heterozygote exon
  - Positive for M694V gene

Patient medical history is representative of patients in clinical practice and has been created for illustrative purposes.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; GI, gastrointestinal; SAA, serum amyloid A; WBC, white blood cell count.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Serious Infections

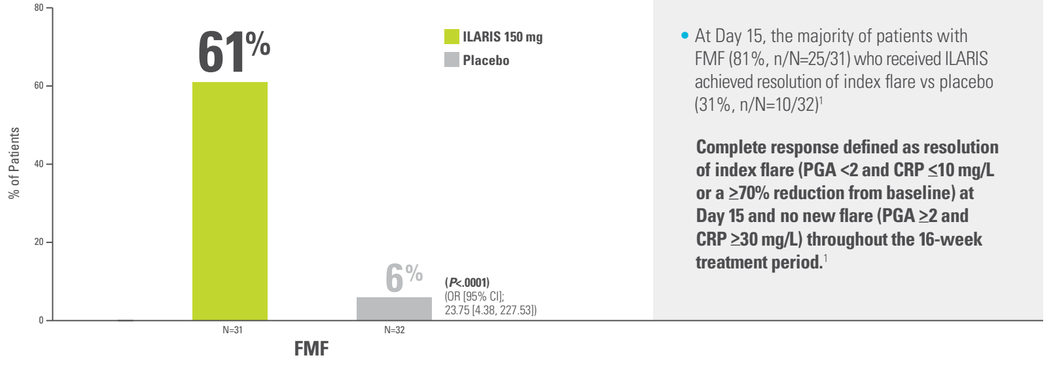
ILARIS has been associated with an increased risk of serious infections. Exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions, which may predispose them to infections. Avoid administering ILARIS to patients during an active infection requiring medical intervention. Discontinue ILARIS if a patient develops a serious infection.

ILARIS® (canakinumab) 150 mg subcutaneous injection

Once-monthly ILARIS demonstrated proven efficacy in patients with FMF[1]

Rapid resolution of index flare at Day 15—with no new flares through Week 16—was achieved by significantly more patients receiving ILARIS[1]

Percent of Patients Achieving Complete Response vs Placebo at Week 16[1]



- At Day 15, the majority of patients with FMF (81%, n/N=25/31) who received ILARIS achieved resolution of index flare vs placebo (31%, n/N=10/32)[1]

Complete response defined as resolution of index flare (PGA <2 and CRP ≤10 mg/L or a ≥70% reduction from baseline) at Day 15 and no new flare (PGA ≥2 and CRP ≥30 mg/L) throughout the 16-week treatment period.[1]

In the clinical trial, patients in the FMF cohort either had **documented active disease despite colchicine** therapy or **documented intolerance to effective doses** of colchicine.[1]

Study Design[1]

The efficacy of ILARIS was assessed in patients with PFS across 3 disease cohorts: FMF, HIDS/MKD, and TRAPS. In the 16-week, double-blind, placebo-controlled treatment period, patients were randomized to receive ILARIS 150 mg (2 mg/kg for a body weight ≤40 kg) subcutaneously or placebo every 4 weeks for 16 weeks and were allowed uptitration to ILARIS 300 mg (or 4 mg/kg) every 4 weeks for patients whose disease flare did not resolve or who had persistent disease, or active treatment.

The primary endpoint was the proportion of complete responders within each cohort as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period.

Patients randomized in the FMF cohort (N=63) were aged 2 to 69 years (median age at baseline: 18.0 years), and of this population, 76.2% did not have fever at baseline. **Randomized FMF patients were those with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine.**

Patients had active disease defined as at least 1 flare per month (median number of flares per year: 18.0) and CRP greater than 10 mg/L (median CRP at baseline: 94.0 mg/L). Patients were allowed to continue their stable dose of colchicine without change. Of the 63 randomized patients, 55 (87.3%) were taking concomitant colchicine therapy on or after randomization.

In the FMF cohort, 10/31 (32.3%) patients randomized to ILARIS 150 mg every 4 weeks received uptitration to 300 mg every 4 weeks during the 16-week treatment period, while 27/32 (84.4%) patients randomized to placebo crossed over to ILARIS.

HIDS, hyperimmunoglobulin D syndrome; MKD, mevalonate kinase deficiency; PGA, Physician's Global Assessment; PFS, periodic fever syndromes; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Serious Infections (cont)

Infections, predominantly of the upper respiratory tract, in some instances serious, have been reported with ILARIS. Generally, the observed infections responded to standard therapy. Isolated cases of unusual or opportunistic infections (eg, aspergillosis, atypical mycobacterial infections, cytomegalovirus, herpes zoster) were reported during ILARIS treatment. A causal relationship of ILARIS to these events cannot be excluded. In clinical trials, ILARIS has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of another interleukin-1 (IL-1) blocker in combination with TNF inhibitors. Coadministration of ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections.

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of new tuberculosis (TB) and reactivation of latent TB. It is possible that use of IL-1 inhibitors, such as ILARIS, increases the risk of reactivation of TB or of opportunistic infections.

ILARIS® (canakinumab) 150 mg subcutaneous injection

Once-monthly ILARIS: Disease activity as measured by PGA[9]

PGA Scores at Baseline to the End of Week 16 in Patients Randomized to ILARIS[9]*
(Proportion of patients in PGA Categories, %)

	Baseline (n=31)	Week 17 (n=31)
Severe	35.5	0
Moderate	54.8	3.2
Mild	9.7	3.2
Minimal	0	19.4
None	0	74.2

A 5-point PGA scale was used by physicians to assess overall disease severity, where 0=no disease-associated signs and symptoms, 1=minimal, 2=mild, 3=moderate, and 4=severe. The key signs and symptoms assessed in the PGA for FMF were abdominal pain, skin rash, chest pain, and arthralgia/arthritis.[9]

Comparisons with placebo from Day 15 onward are limited by the high proportion of patients switching from placebo to canakinumab treatment starting at Day 8.[9]

Exploratory endpoints have not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

Of patients treated with ILARIS 150 mg (n/N=27/31),

87% ❯❯ **SHOWED NO OR MINIMAL SIGNS OF DISEASE ACTIVITY (PGA SCORE <2) AT DAY 15 VS 41% OF PATIENTS TREATED WITH PLACEBO** (n/N=13/32)[1†]

Of patients with FMF receiving ILARIS 150 mg (n/N=28/31),

90% ❯❯ **ACHIEVED CRP LEVELS ≤10 mg/L VS 28% RECEIVING PLACEBO** (n/N=9/32) **AT DAY 15**[1‡]

Of patients with FMF randomized to receive ILARIS 150 mg every 4 weeks (n/N=10/31),

32% ❯❯ **RECEIVED UPTITRATION TO 300 mg EVERY 4 WEEKS**[1,9]

Exploratory Endpoint **Of patients treated with ILARIS** (n/N=22/31), **including those requiring uptitration to 300 mg,**

71% ❯❯ **OVERALL RESPONSE AT WEEK 16**[9§]
Overall response defined as resolution of index flare at Day 29 and no new flare by Week 16 with either the randomized treatment or with an uptitration to 300 mg (4 mg/kg) every 4 weeks before Day 29.

Exploratory endpoints have not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

*This includes patients who were initially randomized to ILARIS 150 mg every 4 weeks. Patients who received uptitration were not included in this endpoint. Comparisons with the placebo arm cannot be made as high proportions of patients switched from placebo to active treatment before Week 16.
†PGA treatment comparison (OR [95% CI]): 10.07 (2.78, 36.49).
‡CRP treatment comparison (OR [95% CI]): 22.51 (5.41, 93.62).
§Comparisons with the placebo arm cannot be made as high proportions of patients switched from placebo to active treatment before Week 16.[9]

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Serious Infections (cont)

Prior to initiating immunomodulatory therapies, including ILARIS, evaluate patients for active and latent TB infection. Appropriate screening tests should be performed in all patients. ILARIS has not been studied in patients with a positive TB screen, and the safety of ILARIS in individuals with latent TB infection is unknown. Treat patients testing positive in TB screening according to standard medical practice prior to therapy with ILARIS. Instruct patients to seek medical advice if signs, symptoms, or high risk exposure suggestive of TB (eg, persistent cough, weight loss, subfebrile temperature) appear during or after ILARIS therapy. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent TB infections before initiating therapy with ILARIS.

ILARIS® (canakinumab) 150 mg subcutaneous injection

Safety profile of ILARIS from FMF, HIDS/MKD, and TRAPS clinical trials[1]

- Overall, there were 58 patients with FMF, 68 patients with HIDS/MKD, and 43 patients with TRAPS in the safety set with a cumulative exposure of 47.61 patient-years. The cumulative exposure in the placebo group was 8.03 patient-years
- The most common adverse reactions (≥10%) were injection site reactions and nasopharyngitis
- Serious infections (eg, conjunctivitis, pneumonia, pharyngitis, pharyngotonsillitis) were observed in approximately 2.4% (0.03 per 100 patient-days) of patients receiving ILARIS

Most Common Adverse Drug Reactions (≥3%) in Patients Treated With ILARIS

Adverse reactions by preferred term in ≥3% of patients with FMF, HIDS/MKD, and TRAPS	ILARIS %
Injection site reactions	10.1
Nasopharyngitis	10.7
Upper respiratory tract infection	7.1
Rhinitis	5.3
Gastroenteritis	3.0
Pharyngitis	3.0

- 0 patients with FMF, 2 patients with HIDS/MKD, and 1 patient with TRAPS discontinued treatment due to AEs[1]

ILARIS is dosed once monthly in patients with FMF[1]

ILARIS Is Given Subcutaneously by a Health Care Professional and Is Dosed According to Body Weight

FMF	≤40 kg	2 mg/kg every 4 weeks	Dose can be increased to 4 mg/kg every 4 weeks*
	>40 kg	150 mg every 4 weeks	Dose can be increased to 300 mg every 4 weeks*

*If clinical response is inadequate.

Refer to the full Prescribing Information for detailed preparation and administration instructions.

ILARIS Companion provides dedicated and dependable support

ILARIS Companion offers a wide range of services and support, including a home health nurse service, and assistance determining specific prior authorization criteria, if required

ILARIS companion
Dedicated and dependable support

Of those who receive that determination,

≈90% of prior authorization (PA) requests are approved[10]

866-972-8315

If you have questions about services, contact a program representative Monday to Friday, 9 AM to 6 PM ET.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Immunosuppression

The impact of treatment with anti-IL-1 therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including ILARIS, may result in an increase in the risk of malignancies.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

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Drugs that affect the immune system by blocking TNF have been associated with an increased risk of new tuberculosis (TB) and reactivation of latent TB. It is possible that use of IL-1 inhibitors, such as ILARIS, increases the risk of reactivation of TB or of opportunistic infections.

Prior to initiating immunomodulatory therapies, including ILARIS, evaluate patients for active and latent TB infection. Appropriate screening tests should be performed in all patients. ILARIS has not been studied in patients with a positive TB screen, and the safety of ILARIS in individuals with latent TB infection is unknown. Treat patients testing positive in TB screening according to standard medical practice prior to therapy with ILARIS. Instruct patients to seek medical advice if signs, symptoms, or high risk exposure suggestive of TB (eg, persistent cough, weight loss, subfebrile temperature) appear during or after ILARIS therapy. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent TB infections before initiating therapy with ILARIS.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Immunosuppression

The impact of treatment with anti-IL-1 therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including ILARIS, may result in an increase in the risk of malignancies.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with ILARIS. During clinical trials, no anaphylactic reactions attributable to treatment with canakinumab have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), characterized by serious skin eruptions, has been reported in patients with autoinflammatory conditions treated with ILARIS. If a severe hypersensitivity reaction occurs, immediately discontinue ILARIS; treat promptly and monitor until signs and symptoms resolve.

Immunizations

Avoid administration of live vaccines concurrently with ILARIS. Update all recommended vaccinations prior to initiation of therapy with ILARIS. In addition, because ILARIS may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ILARIS.

Canakinumab, like other monoclonal antibodies, is actively transported across the placenta mainly during the third trimester of pregnancy and may cause immunosuppression in the *in utero* exposed infant. The risks and benefits should be considered prior to administering live vaccines to infants who were exposed to ILARIS *in utero* for at least 4 to 12 months following the mother's last dose of ILARIS.

Macrophage Activation Syndrome

Macrophage Activation Syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease, and should be aggressively treated. Physicians should be attentive to symptoms of infection or worsening of Still's disease as these are known triggers for MAS. Eleven cases of MAS were observed in 201 SJIA patients treated with canakinumab in clinical trials. Based on the clinical trial experience, ILARIS does not appear to increase the incidence of MAS in Still's disease patients, but no definitive conclusion can be made.

ADVERSE REACTIONS

Serious adverse reactions reported with ILARIS in the CAPS clinical trials included infections and vertigo. The most common adverse reactions greater than 10% associated with ILARIS treatment in CAPS patients were nasopharyngitis, diarrhea, influenza, rhinitis, headache, nausea, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo.

The most common adverse reactions greater than or equal to 10% reported by patients with TRAPS, HIDS/MKD, and FMF treated with ILARIS were injection site reactions and nasopharyngitis.

The most common adverse drug reactions greater than 10% associated with ILARIS treatment in SJIA patients were infections (nasopharyngitis and upper respiratory tract infections), abdominal pain, and injection site reactions.

The most common adverse reactions greater than 2% reported by adult patients with gout flares treated with ILARIS in clinical trials were nasopharyngitis, upper respiratory tract infections, urinary tract infections, hypertriglyceridemia, and back pain.

References: 1. Ilaris. Prescribing information. Novartis Pharmaceuticals Corp. **2.** Jesus AA, Oliveira JB, Hilário MO, et al. Pediatric hereditary autoinflammatory syndromes. *J Pediatr (Rio J).* 2010; 86(5):353-366. doi:10.2223/JPED.2015 **3.** Hoffman HM, Simon A. Recurrent febrile syndromes — what a rheumatologist needs to know. *Nat Rev Rheumatol.* 2009;5(5):249-256. doi:10.1038/nrrheum.2009.40 **4.** Barron KS, Kastner DL. Periodic fever syndromes and other inherited autoinflammatory diseases. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, eds. *Textbook of Pediatric Rheumatology.* 7th ed. Elsevier; 2016:609-626. **5.** Kastner DL. Hereditary periodic fever syndromes. *Hematology Am Soc Hematol Educ Program.* 2005(1):74-81. doi:10.1182/asheducation-2005.1.74 **6.** Ciccarelli F, De Martinis M, Ginaldi L. An update on autoinflammatory diseases. *Curr Med Chem.* 2014;21(3):261-269. doi:10.2174/09298673113206660303 **7.** Zadeh N, Getzug T, Grody WW. Diagnosis and management of familial Mediterranean fever: integrating medical genetics in a dedicated interdisciplinary clinic. *Genet Med.* 2011;13(3):263-269. doi:10.1097/GIM.0b013e31820e27b1 **8.** Samuels J, Aksentijevich I, Torosyan Y, et al. Familial Mediterranean fever at the millennium clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. *Medicine (Baltimore).* 1998;77(4):268-297. doi:10.1097/00005792-199807000-00005 **9.** Data on file. CACZ885N2301 FMF, HIDS/MKD, and TRAPS Clinical Study Report. Novartis Pharmaceuticals Corp; 2016. **10.** Data on file. ILARIS Companion CRM Statistics Updates 2023. Novartis Pharmaceuticals Corp; 2023.

ILARIS® (canakinumab)
150 mg subcutaneous injection

ILARIS HAS A DEMONSTRATED EFFICACY AND SAFETY PROFILE IN PATIENTS WITH FMF

A clinical trial for ILARIS included FMF patients with active disease despite colchicine therapy or intolerant to effective doses of colchicine

Once-monthly dosing for ILARIS in patients with FMF

ILARIS is indicated to treat 8 autoinflammatory diseases across Still's disease, PFS, and gout flares

- Still's disease: SJIA and AOSD
- PFS: FMF, HIDS/MKD, TRAPS, CAPS (FCAS and MWS)

AOSD, adult-onset Still's disease; CAPS, cryopyrin-associated periodic syndromes; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; SJIA, systemic juvenile idiopathic arthritis.

For more information, visit **www.ILARISHCP.com**

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ILARIS® (canakinumab) 150 mg subcutaneous injection