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Ilaris - Safety profile - in Stills - HCP

Prescribing information

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ILARIS® (canakinumab) safety profile in Still’s disease

Indications[1]

Periodic fever syndromes
ILARIS is indicated for the treatment of the following autoinflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older:

- Cryopyrin-associated periodic syndromes (CAPS), including:

    - Muckle-Wells syndrome (MWS)
    - Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological, cutaneous, articular syndrome (CINCA)
    - Severe forms of familial cold autoinflammatory syndrome (FCAS)/familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS)
- Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)
- Familial Mediterranean Fever (FMF)
    - ILARIS should be given in combination with colchicine, if appropriate

Still's disease
ILARIS is indicated in patients who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids, for the treatment of active Still's disease, including:

- Adult-onset Still's disease (AOSD)
- Systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older
- ILARIS can be given as monotherapy or in combination with methotrexate

Gouty arthritis
ILARIS is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal 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.

Key safety profile data for ILARIS in the treatment of adult-onset Still's disease **(AOSD)** and systemic juvenile idiopathic arthritis **(SJIA)**.

Paediatric population
CAPS, TRAPS, HIDS/MKD and **FMF:** The safety and efficacy of canakinumab in CAPS, TRAPS, HIDS/MKD, and FMF patients under 2 years of age have not been established. Currently available data are described in the SmPC, but no recommendation on a posology

can be made.

SJIA: The safety and efficacy of canakinumab in SJIA patients under 2 years of age have not been established. No data are available.

Please refer to the ILARIS Summary of Product Characteristics (SmPC) for full safety information.[1]

- The most frequent adverse drug reactions were infections predominantly of the upper respiratory tract. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment[1]

- Hypersensitivity reactions have been reported in patients treated with canakinumab[1]

- Opportunistic infections have been reported in patients treated with canakinumab (please see 'Special warnings and precautions for use' below)[1]

Tabulated list of adverse reactions

MedDRA System Organ Class	Indications: CAPS, TRAPS, HIDS/MKD, FMF, SJIA
Infections and infestations	
Very common	Respiratory tract infections (including pneumonia, bronchitis, influenza, viral infection, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infection) Ear infection Cellulitis Gastroenteritis Urinary tract infection
Common	Vulvovaginal candidiasis
Nervous system disorders	
Common	Dizziness/vertigo
Gastrointestinal disorders	
Very common	Upper abdominal pain*
Skin and subcutaneous tissue disorders	
`Very common	Injection site reaction
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia*
Common	Musculoskeletal pain*
Investigations	

MedDRA System Organ Class	Indications: CAPS, TRAPS, HIDS/MKD, FMF, SJIA
Very common	Creatinine renal clearance decreased*[†] Proteinuria*[‡] Leukopenia* (see ’Laboratory anomalies’ below)
Common	Neutropenia (see ’Laboratory anomalies’ below)
Uncommon	Platelet count decreased (see ’Laboratory anomalies’ below)

Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*In SJIA.
[†]Based on estimated creatinine clearance, most were transient.
[‡]Most represented transient trace to 1+ positive urinary protein by dipstick.

Adapted from ILARIS® (canakinumab) Summary of Product Characteristics.[1]

- AOSD
- SJIA

- This data from the Phase II CONSIDER study showed that the overall safety findings were consistent with the known profile of ILARIS[1]

- The safety analyses were based on all patients randomised who received at least one dose of the study drug[2]

- Within the first 12-week period of this trial, two patients experienced an SAE, both of them under treatment with Ilaris (increased liver enzymes and patellofemoral pain syndrome leading to hospitalisation)[2]

- A further seven SAEs were observed in the second period of the study (between Weeks 12 and 24): two in Ilaris-exposed patients (deep vein thrombosis and

hypotonia) and the other five in one patient treated with placebo (fracture at MCP 5, hand fracture, removal of a medical device at MCP 5, upper abdominal pain and acute cholecystitis)[2]

- Due to premature termination of the study, observation time was limited to a maximum of 27 months (reached only by one patient)[2]
- Primary endpoint of the study (proportion of patients with a clinically relevant reduction of the articular manifestation measure by change in disease activity score) at Week 12 was not met[2]
- This data provides long-term (up to 5 years) safety information on a pooled population from Ilaris' clinical programme in SJIA[3]
- Overall, the median duration of exposure (canakinumab and placebo) in was 3.5 years[3]
- Long-term use of Ilaris was generally well tolerated and consistent with the safety profile that has been reported in other Ilaris trials[3]
- Infections were the most common adverse events (AEs)[3]
- Despite disease control, new macrophage activation syndrome (MAS) events occurred while on Ilaris therapy[3]

Special populations[1]

Canakinumab has not been studied in patients with hepatic impairment. No recommendation on a posology can be made.

No dose adjustment is needed in patients with renal impairment. However, clinical experience in such patients is limited.

Contraindications[1]

- Hypersensitivity to the active substance or to any of the following excipients: mannitol, histidine, histidine hydrochloride monohydrate, polysorbate 80, water for injections
- Active, severe infections

Special warnings and precautions for use[1]

Infections
Canakinumab is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with canakinumab. Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections. Canakinumab should not be initiated or continued in patients during an active infection requiring medical intervention.

Tuberculosis screening
In approximately 12% of CAPS patients tested with a PPD (purified protein derivative) skin test in clinical trials, follow-up testing yielded a positive test result while treated with canakinumab without clinical evidence of a latent or active tuberculosis infection. It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as canakinumab increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection.

Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with canakinumab. All patients should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, subfebrile temperature) appear during canakinumab therapy.

Neutropenia and leukopenia
Neutropenia (absolute neutrophil count [ANC] $<1.5 \times 10^9$/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including canakinumab. Treatment with canakinumab should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months.

If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies
Malignancy events have been reported in patients treated with canakinumab. The risk for the development of malignancies with antiinterleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions
Hypersensitivity reactions with canakinumab therapy have been reported. The majority of these events were mild in severity. During clinical development of canakinumab in over 2600 patients, no anaphylactoid or anaphylactic reactions attributable to treatment with canakinumab were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded.

Hepatic function
Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials.

Vaccinations
No data are available on the risk of secondary transmission of infection by live (attenuated) vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks.

Prior to initiation of canakinumab therapy it is recommended that adult and paediatric patients receive all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine.

Mutation in NLRP3 gene in CAPS patients
Clinical experience in CAPS patients without a confirmed mutation in the NLRP3 gene is limited.

Macrophage activation syndrome in patients with Still's disease (SJIA and AOSD)
Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Based on clinical trial experience, canakinumab does not appear to increase the incidence of MAS in Still's disease patients, but no definitive conclusion can be made.

Drug reaction with eosinophilia and systemic symptoms (DRESS)
DRESS has rarely been reported in patients treated with ILARIS, predominantly in patients with SJIA. Patients with DRESS may require hospitalisation, as this condition may be fatal. If signs and symptoms of DRESS are present and an alternative aetiology cannot be established, canakinumab should not be re-administered and a different treatment considered.

Fertility, pregnancy and lactation[1]

Women should use effective contraceptives during treatment with canakinumab and for up to 3 months after the last dose.

The risk for the foetus/mother is unknown. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit–risk evaluation. Women who received canakinumab during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their newborn infant.

The decision whether to breastfeed during canakinumab therapy should therefore only be taken after a thorough benefit–risk evaluation.

Laboratory abnormalities[1]

Laboratory abnormalities in SJIA patients
Haematology: In the overall SJIA programme, transient decreased white blood cell (WBC) counts ≤ 0.8 x LLN were reported in 33 patients (16.5%). Transient decreases in absolute neutrophil count (ANC) to less than 1 x 10^9/l were reported in 12 patients (6.0%). Transient decreases in platelet counts (< LLN) were observed in 19 patients (9.5%).
ALT/AST: In the overall SJIA programme, high ALT and/or AST > 3 x upper limit of normal (ULN) were reported in 19 patients (9.5%).

Interactions between canakinumab and other medicinal products have not been investigated in formal studies. Please see the SmPC for full details on interactions.

Please refer to the SmPC for more information and the full list of special

warnings and precautions for use.[1]

AE, adverse event; ANC, absolute neutrophil count; AOSD, adult-onset Still's disease; CAPS, cryopyrin-associated periodic syndromes; CINCA, chronic infantile neurological, cutaneous, articular syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; FCAS, familial cold autoinflammatory syndrome; FCU, familial cold urticaria; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; LLN, lower limit normal; MAS, macrophage activation syndrome; MedDRA PT, Medical Dictionary for Regulatory Activities preferred term; MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAID, non-steroidal anti-inflammatory drug; SJIA, systemic juvenile idiopathic arthritis; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; WBC, white blood cell count.

References

1. ILARIS® (canakinumab) Summary of Product Characteristics.

2. Kedor C, et al. *Ann Rheum Dis* 2020;79(8):1090–1097 and supplementary appendix.

3. Ruperto N, et al. *Ann Rheum Dis* 2018;77(12):1710–1719.

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Resources for HCPs

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report, or alternatively email medinfo.uk@novartis.com or call 01276 698370.
