Regulatory Affairs

Ilaris

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Canakinumab
Product(s) concerned (brand name(s)):	Ilaris
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Summary of the risk management plan for Ilaris

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ilaris is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Ilaris Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ilaris

This is a summary of the risk management plan for canakinumab (Ilaris). The RMP details important risks of canakinumab (Ilaris), how these risks can be minimized, and how more information will be obtained about canakinumab's (Ilaris) risks and uncertainties (missing information). Canakinumab (Ilaris) EU summary of product characteristics (EU SmPC) and its package leaflet provide essential information to healthcare professionals and patients on how canakinumab (Ilaris) should be used. This summary of the RMP for canakinumab (Ilaris) should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of the canakinumab (Ilaris) RMP.

I. The medicine and what it is used for

Canakinumab (Ilaris) is authorized for periodic fever syndromes, gouty arthritis, and Still's disease in the EEA (see EU SmPC for the full indications). It contains canakinumab as the active substance and it is given in the form of 150 mg powder for solution for injection and 150 mg/ml solution for injection. Further information about the evaluation of canakinumab's (Ilaris) benefits can be found in canakinumab's (Ilaris) EPAR, including in its plain-language summary, available on the EMA website (https://www.ema.europa.eu/en/medicines)

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of canakinumab (Ilaris), together with measures to minimize such risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and Information for Professionals addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures. In the case of canakinumab (Ilaris), these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary.

These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of canakinumab's (Ilaris) is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of canakinumab (Ilaris) are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of canakinumab (Ilaris). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information

Important identified risks	Infections (including opportunistic infections) Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (forStill's disease) Canakinumab – immunosuppressants combination therapy toxicity
Important potential risks	Malignancy Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis) Macrophage activation syndrome (for Still's disease) Interactions with vaccines Drug Reaction with Eosinophilia and Systemic Symptoms(DRESS)
Missing information	Effects on growth (for periodic fever syndromes and Still's disease)

II B: Summary of important risks

Important identified risk: Infections (including opportunistic infections)

Evidence for linking the riskto the medicine	IL-1 is a pro-inflammatory cytokine secreted by macrophages and dendritic cells. It enhances the immune response (activation and proliferation of T andB cells upon antigen stimulation), the inflammatory process and haematopoiesis. Inhibiting IL-1 could therefore have an effect on the immuneresponse against bacteria and other infectious agents. Given the biologic plausibility and the well-characterized risk of infections in the marketed indications (CAPS, TRAPS, HIDS/MKD, FMF, Still's disease, Gouty arthritis), infections are not unexpected. In CANTOS, the large double-blind phase 3 study in prevention of the occurrence of cardiovascular events,serious infections were reported slightly more frequently in canakinumab treated patients compared to placebo. Opportunistic infections have occasionally been reported in patients treated with canakinumab in the marketed indications and, theoretically, inhibition of IL-1 may increase the risk of opportunistic infection. However, in CANTOS, alarge double-blind phase 3 study, the rate of confirmed opportunistic infections, including TB, was very low and comparable across the treatment groups, including placebo. Most of the cases of non-tuberculous opportunistic

	infection were confounded and all cases of confirmed TB occurred in patients in TB-endemic areas. There were no cases of reactivation of TB.
Risk factors and risk groups	In CANTOS, the pattern of Infection AEs and SAEs in the different subgroupsbased on age, sex, race, ethnicity, region, time since index MI, BMI, medical history of gout, co-existing T2DM and baseline hsCRP level was generally consistent with that observed for the overall population. Subgroups generally considered at higher risk for infections (the elderly and diabetic patients) had an increased incidence of infections in CANTOS compared with patients in subgroups considered to be at lower risk but with a pattern of between- treatment differences that was comparable to that observed in the overall population. There was no evidence of increased incidence of infection with canakinumab in the elderly. However, cellulitis and infectious pneumonia were more frequent in patients with diabetes and asthma/COPD, respectively, than in patients without these conditions.
Risk minimization measures	Addressed in EU SmPC in: Section 4.3 (Contraindication), Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) and Section 4.8 (Undesirable effects-summary of the safety profile) Additional risk minimization activities: Patient reminder card
Additional pharmacovigilance activities	Study G2403: SJIA Registry

Important identified risk: Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)

Evidence for linking the riskto the medicine	Mechanism of action is not known. For bilirubin elevations: Displacementfrom carrier proteins (reduced with anti-inflammatory effect). Current evidence is based on a clinical data, literature, and post marketing experience.
Risk factors and risk groups	Unknown.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).
Additional pharmacovigilance activities	Study G2403: SJIA Registry

Important identified risk: Canakinumab – immunosuppressants combination therapy toxicity

Evidence for linking the riskto the medicine	Canakinumab binds to and neutralizes the activity of human IL-1β, a pro-inflammatory cytokine. Hence, any other drugs targeting the immune systemmay lead to a synergistic immune suppression. Current evidence is based on literature, clinical trial, and post marketing experience.
Risk factors and risk groups	Concomitant treatment with one or more biologics or immunosuppressantdrugs along with canakinumab increases the risk to infection.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warning and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction)

Additional pharmacovigilance activities	Study G2403: SJIA Registry

Important potential risk: Malignancy

Evidence for linking the riskto the medicine	Immunosuppression could potentially lead to an increase in the risk for malignancies. However, canakinumab is not a broad-spectrum immunosuppressant that severely impairs tumor surveillance or anti-tumor immune mechanisms. A hypothetical risk which is based on potential mechanistic plausibility, although the growing body of evidence suggests that IL-1β has a more likely role in tumor promotion rather than in antitumor immunity. No evidence supporting this risk was observed in CANTOS but rather a lower incidence ofreported overall malignancy events and lung cancer events in particular wereobserved in this large double-blind phase 3 study.
Risk factors and risk groups	In a JIA cohort in Sweden malignancies were identified. The incidence wasfound to be 0.46 cases per 1000 person years. Patients with SJIA were at increased risk of lymphoproliferative malignancies and overall cancers as well.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)
Additional pharmacovigilance activities	Study G2403: SJIA Registry

Important potential risk: Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromesand gouty arthritis)

Evidence for linking the riskto the medicine	Mechanism of action is not known. For bilirubin elevations: Displacementfrom carrier proteins (reduced with anti-inflammatory effect). Current evidence is based on a clinical data, literature, and post marketing experience.
Risk factors and risk groups	Unknown.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).
Additional pharmacovigilance activities	Study G2403: SJIA Registry

Important potential risk: Macrophage activation syndrome (for Still's disease)

Evidence for linking the riskto the medicine	Unknown
Risk factors and risk groups	Patients with Still's disease, systemic lupus erythematosus and Kawasaki disease are at highest risk, although MAS has been reported in patients withany rheumatic condition.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) Additional risk minimization activities: Patient reminder card
Additional pharmacovigilance activities	Study G2403: SJIA Registry

Important potential risk: Interactions with vaccines

Evidence for linking the riskto the medicine	Interactions with vaccines: Since the drug may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving canakinumab. Current evidence is based on a clinical data, literature, and post marketing experience.
Risk factors and risk groups	Since this is a potential risk, no attributable risk increase due to canakinumabhas been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) and Section 4.5 (interaction with other medicinal products and other forms of interaction) Additional risk minimization activities: Patient reminder card

Important potential risk: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Evidence for linking the riskto the medicine	Current evidence is based on literature, and post marketing experience forthis class effect risk.
Risk factors and risk groups	All 13 cases of DRESS occurring in Ilaris-treated patients were reported in pediatric patients, twelve of whom had underlying SJIA and one with autoinflammatory disease not further specified.
Risk minimization measures	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)

Important missing information: Effects on growth (for periodic fever syndromes and Still’s disease)

Risk minimization measures	Study G2403: SJIA Registry

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II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization of canakinumab (Ilaris)and all specific obligations have been fulfilled.

II.C.2. Other studies in post-authorization development plan

Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study G2403: SJIA registry	To collect prospective safety, tolerability, efficacy, and treatment adherence information on systemic juvenile idiopathic arthritis (SJIA) subjects participating in the CARRA registry