NOVARTIS

Ilaris®

Interleukin – 1 beta inhibitors.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Powder for solution for injection.

The powder is a white lyophilisate.

Active substance

Each vial contains 150 mg of canakinumab (plus 30mg of canakinumab (20%) as overfill).

Canakinumab is a recombinant fully human monoclonal antibody expressed in mouse myeloma Sp2/0 cell.

Excipients

Sucrose, L-Histidine, L-Histidine HCl monohydrate, Polysorbate 80.

INDICATIONS

Cryopyrin-Associated Periodic Syndromes (CAPS)

Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children aged 2 years and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS) /Familial Cold Urticaria (FCU),
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA).

Systemic Juvenile Idiopathic Arthritis (SJIA)

Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with NSAIDS and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen for CAPS

The recommended starting dose of Ilaris for CAPS patients is

Adults and children ≥4 years of age:

- 150 mg with body weight >40 kg
- 2 mg/kg with body weight ≥15 kg and ≤40 kg
- 4mg/kg with body weight ≥7.5 kg and <15 kg

Children 2 to <4 years of age:

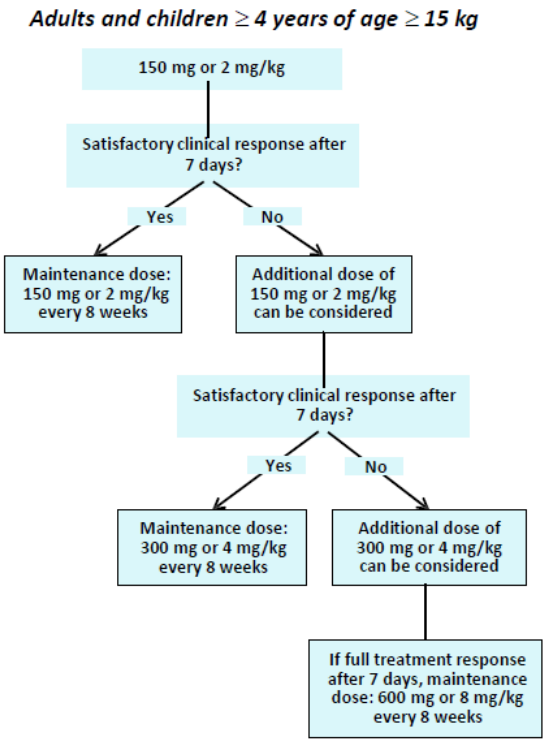
- 4 mg/kg for patients with body weight ≥7.5 kg

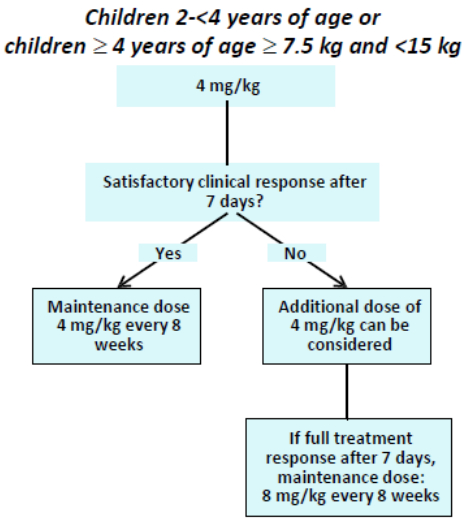
This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, Iif a satisfactory clinical response (resolution of rash and other generalized inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of Ilaris at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg andor 4 mg/kg every 8 weeks should be maintained. If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of ILARIS at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be maintained. No experience exists for doses >600mg every 8 weeks.

For patients with a starting dose of 4mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of ILARIS 4 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 8 mg/kg every 8 weeks should be maintained.

Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited.





Dosage regimen for SJIA

The recommended dose of Ilaris for SJIA patients with body weight ≥7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection.

Special populations

Renal impairment

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

Hepatic impairment

Ilaris has not been specifically studied in patients with hepatic impairment. Since Ilaris is a human IgG immunoglobulin, hepatic impairment is not expected to impact its pharmacokinetics.

Pediatric patients

The safety and efficacy of Ilaris in CAPS and SJIA patients under 2 years of age have not been established.

Geriatric patients

Clinical experience in patients above 65 years is limited, therefore caution is recommended.

Method of administration

Subcutaneous injection.

After proper training in injection technique, patients or caregivers may inject Ilaris if their physician determines that it is appropriate and with medical follow-up as necessary (see section PHARMACEUTICAL INFORMATION, INSTRUCTIONS FOR USE AND HANDLING).

CONTRAINDICATIONS

Confirmed hypersensitivity to the active substance or to any of the excipients. (See section WARNINGS AND PRECAUTIONS and section ADVERSE DRUG REACTIONS)

Active, severe infections (see section WARNINGS AND PRECAUTIONS)

WARNINGS AND PRECAUTIONS

Infections

Ilaris is associated with an increased incidence of serious infections. Physicians should exercise caution when administering Ilaris to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections.

Treatment with Ilaris should not be initiated or continued in patients with active infection requiring medical intervention.

Infections, predominantly of the upper respiratory tract, in some instances serious, have been reported more frequently with Ilaris than with placebo treatment. All infections responded to standard therapy. In canakinumab-treated patients with serious and systemic infections, a physiological inflammatory response was maintained as evidenced by concomitant C-reactive protein (CRP) elevation and fever. A blunted inflammatory response to infections cannot be excluded and increased vigilance is therefore recommended.

Isolated cases of unusual or opportunistic infections (including aspergillosis, atypical mycobacterial infections, herpes zoster) have been reported during Ilaris treatment. A causal relationship of Ilaris to these events cannot be excluded.

Concomitant use of Ilaris with tumor necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section INTERACTIONS).

In approximately 12% of CAPS patients tested with a PPD skin test in clinical trials, follow-up testing yielded a positive test result while treated with Ilaris without clinical evidence of a latent or active tuberculosis infection

It is unknown whether the use of IL-1 inhibitors such as Ilaris increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests e.g. tuberculin skin test, Interferon-Gamma-Release-Assay (IGRA) or chest X-ray should be performed in all patients (local recommendations may apply). Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with Ilaris. 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 Ilaris therapy In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Malignancies

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

Hypersensitivity reactions

Hypersensitivity reactions with Ilaris therapy have been reported. The majority of these events were mild in severity. During clinical development of Ilaris in over 2,300 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. (see section CONTRAINDICATIONS and section ADVERSE DRUG REACTIONS)

Vaccinations

No data are available on the risk of secondary transmission of infection by live (attenuated) vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks (see section INTERACTIONS and also section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Prior to initiation of Ilaris therapy, adult and paediatric patients should receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine.

Neutropenia and leukopenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including Ilaris. Treatment with Ilaris 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. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Macrophage activation syndrome (in SJIA patients)

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA, and should be aggressively treated. Physicians should be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for MAS. Based on clinical trial experience, Ilaris does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.

Mutation in NLRP3 gene

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

ADVERSE DRUG REACTIONS

Summary of the safety profile

Over 2,300 subjects including approximately 250 children (aged 2 to 17 years) have been treated with Ilaris in interventional studies in CAPS, SJIA, gouty arthritis or other IL-1beta mediated diseases, and healthy volunteers. The most frequently reported adverse drug reactions were infections, predominantly of the upper respiratory tract. The majority of the events were mild to moderate although serious infections were observed. No impact on the type or frequency of adverse events was seen with longer-term treatment.

Hypersensitivity reactions have been reported in patients treated with Ilaris (see section CONTRAINDICATIONS and section WARNINGS AND PRECAUTIONS).

Opportunistic infections have been reported in patients treated with ILARIS (see section WARNINGS AND PRECAUTIONS).

CAPS

A total of 194 adult and paediatric CAPS patients (including FCAS/FCU, MWS, and NOMID/CINCA) have received Ilaris in clinical trials. The safety of Ilaris compared with placebo was investigated in a pivotal phase III trial that consisted of an 8-week, open-label period (Part I), a 24-week, randomised, double-blind and placebo-controlled withdrawal period (Part II), and a 16-week open label period on Ilaris (Part III). All patients were treated with Ilaris 150 mg subcutaneous or 2 mg/kg if body weight was ≥15 kg and ≤40 kg (see section CLINICAL STUDIES). Safety data from 194 CAPS patients is available. A total of 10 serious adverse reactions that were considered by the investigator as related to treatment were reported during the clinical programme in CAPS, of which the most frequent events were infections (3) and vertigo (2).

Adverse reactions are listed according to MedDRA system organ class and frequency category. 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.

Table 1 Tabulated summary of reported adverse drug reactions from pivotal CAPS clinical trial

		Part I	Part II		Part III
		Ilaris N=35	Ilaris N=15	Placebo	Ilaris N=31
		n (%)	n (%)	N=16 n (%)	n (%)
Infections and infestations					
Very common	Nasopharyngitis	4 (11.4%)	5 (33.3%)	3 (18.8%)	4 (12.9%)
Common	Urinary tract infection	0	2 (13.3%)	0	1 (3.2%)
	Upper respiratory tract infection	1 (2.9%)	1 (6.7%)	1 (6.3%)	1 (3.2%)
	Viral infection	3 (8.6%)	2 (13.3%)	3 (18.7%)	1 (3.2%)
Skin and subcutaneous tissue disorders					
Very common	Injection site reaction	3 (8.6%)	2 (13.3%)	1 (6.3%)	1 (3.2%)
Nervous system disorders					
Very common	Dizziness/Vertigo	3 (8.6%)	0	0	3 (9.7%)

Solicited through physician questionaires

- All events resolved despite continued treatment with Ilaris.

In the long-term, open label studies with dose-escalation, events of infections (gastroenteritis, respiratory tract infection, and upper respiratory tract infection), vomiting and dizziness were more frequently reported in the 600 mg or 8 mg/kg dose group than in other dose groups

Laboratory abnormalities (CAPS)

Haematology

During clinical trials with Ilaris mean values for hemoglobin increased and for white blood cell, neutrophils and platelets decreased.

Hepatic transaminases

Elevations of transaminases have been observed rarely in CAPS patients.

Bilirubin

Asymptomatic and mild elevations of serum bilirubin have been observed in CAPS patients treated with Ilaris without concomitant elevations of transaminases.

Pediatric patients

There were 69 pediatric CAPS patients with an age range from 2 years to 17 years. Overall, there were no clinically meaningful differences for the safety and tolerability profile of ILARIS in pediatric patients compared to the overall CAPS population (comprised of adult and pediatric patients, N=194) including the overall frequency and severity of infectious episodes in pediatric patients were comparable to that in the adult population. Infections of the upper respiratory tract were the most frequently reported infection events.

SJIA

A total of 201 SJIA patients aged 2 to <20 years have received Ilaris in clinical trials. The safety of Ilaris compared to placebo was investigated in two pivotal phase III studies (see section CLINICAL STUDIES).

Adverse reactions are listed according to MedDRA version 15.0 system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency category with the most common first. 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.

Table 2 Tabulated summary of adverse drug reactions from pivotal SJIA clinical trials

	G2301			G2305		Frequency category
	Part I	Part II				
	Ilaris N=177 n (%)	Ilaris N=50 n (%)	Placebo N=50 n (%)	Ilaris N=43 n (%)	Placebo N=41 n (%)	
Infections and infestations						
Infection (e.g. nasopharyngitis, (viral) upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)	97 (54.8%)	27 (54%)	19 (38%)	13 (30.2%)	5 (12.2%)	Very common
Gastrointestinal disorders						
Abdominal pain (upper)	25 (14.1%)	8 (16%)	6 (12%)	3 (7%)	1 (2.4%)	Very common
Skin and subcutaneous tissue disorders						
Injection site reaction*						
mild	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)	Very common
moderate	2 (1.1%)	1 (2.0%)	0	0	0	Common

** No injection site reaction led to study discontinuation*

Laboratory abnormalities (SJIA)

Hematology

Decreased white blood cell counts (WBC) ≤0.8× lower limit of normal (LLN) were reported in 5 patients (10.4%) in the Ilaris group compared to 2 (4.0%) in the placebo group.

Transient decreases in absolute neutrophils counts (ANC) to less than $1x10^9$/L were reported in 3 patients (6.0%) in the Ilaris group compared to 1 patient (2.0%) in the placebo group. One case of ANC counts <$0.5x10^9$/L was observed in the Ilaris group and none in the placebo group (see section WARNINGS AND PRECAUTIONS).

Mild (<LLN and >$75x10^9$/L) and transient decreases in platelet counts were observed in 3 (6.3%) Ilaris treated patients versus 1 (2.0%) placebo-treated patient.

Hepatic transaminases

ALT/AST

High ALT and/or AST >3× upper limit of normal (ULN) were reported in 2 (4.1%) Ilaris-treated patients and 1 (2.0%) placebo patient. All patients had normal values at the next visit.

INTERACTIONS

Interactions between Ilaris and other medicinal products have not been investigated in formal studies.
The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be normalised when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of Ilaris with TNF inhibitors is not recommended because this may increase the risk of serious infections.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris. It is recommended that, if possible, pediatric and adult patients should complete all immunisations in accordance with current immunisation guidelines prior to initiating Ilaris therapy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

The results of a study in healthy adult subjects demonstrated that a single dose of Ilaris 300 mg does not affect the induction and persistence of antibody responses after vaccination with influenza and glycosylated protein based meningococcus vaccines.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There is a limited amount of data from literature and post-marketing reports on the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section Animal data). The risk for the fetus/mother is unknown. Women should use effective contraceptives during treatment with Ilaris and for up to 3 months after the last dose. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.

Clinical considerations

Monoclonal antibodies such as canakinumab actively cross the placenta and are detectable in the fetus, predominantly in the second and third trimesters of pregnancy. Based on limited human data, canakinumab levels were detected in cord and neonatal blood. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab in utero is not recommended for 16 weeks following the mother's last dose of Ilaris before childbirth.

Animal data

In an embryo-fetal development study in marmosets canakinumab showed no maternal toxicity, embryo-toxicity or teratogenicity when administered throughout organogenesis. In addition, canakinumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation.

No undesirable effects of a murine anti-murine IL-1 beta antibody were seen in a complete set of reproductive studies in mice. In addition, no effects on labor and delivery were observed. The high dose used in these studies was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity.

Lactation

Risk summary

It is not known whether canakinumab is transferred into breast milk. There are no data on the effects of Ilaris on the breastfed child or the effects of Ilaris on milk production. Animal studies have shown that a murine anti-murine IL-1beta antibody had no undesirable effects on development in nursing mouse pups

Breast-feeding is not recommended during treatment with Ilaris therapy.

Females and males of reproductive potential

There is a limited amount of data from the use of canakinumab in females of reproductive potential.

Infertility

Formal studies of the potential effect of Ilaris on human fertility have not been conducted.

Canakinumab had no effect on male fertility parameters in marmoset (*C. jacchus*). A murine anti-murine IL-1beta antibody had no undesirable effects on fertility in male or female mice.

OVERDOSAGE

There is limited experience with overdosage. In early clinical trials, patients and healthy volunteers received doses as high as 10mg/kg administered intravenously or subcutaneously without evidence of acute toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted as necessary

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Interleukin inhibitors, ATC code: L04AC08

Mechanism of action (MOA)

Canakinumab is a fully human monoclonal anti-human interleukin-1beta (IL-1beta) antibody of the IgG1/kappa isotype. Canakinumab binds with high affinity specifically targeting human IL-1beta and neutralizes the biological activity of human IL-1beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1beta-induced gene activation and the production of inflammatory mediators.

Pharmacodynamics (PD)

Excess production of IL-1 beta in inflammatory diseases can lead to local or systemic inflammation, increased production of C-reactive protein (CRP) or serum amyloid A (SAA), and fever.

CAPS

CAPS patients who have uncontrolled over-production of IL-1 beta show a rapid response to therapy with canakinumab, i.e. laboratory parameters such as high CRP and SAA, high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

SJIA

Systemic Juvenile Idiopathic Arthritis is a severe autoinflammatory disease, driven by innate immunity by means of pro-inflammatory cytokines, a key one being interleukin 1beta (IL-1beta).

Common features of SJIA include fever, rash, hepatosplenomegaly, lymphadenopathy, polyserositis and arthritis. Treatment with canakinumab resulted in a rapid and sustained improvement of both the articular and the systemic features of SJIA with significant reduction of the number of inflamed joints, prompt resolution of fever and reduction of acute phase reactants in the majority of patients (see section CLINICAL STUDIES).

Pharmacokinetics (PK)

Absorption

The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single subcutaneous administration of 150 mg in adult CAPS patients. The mean terminal half-life was 26 days. Based on a population pharmacokinetic analysis in the CAPS population including children from 2 years of age, the absolute bioavailability of subcutaneous administration of canakinumab was estimated to be 66 %. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as intravenous infusion or from 150 to 600 mg as subcutaneous injection.

Distribution

Canakinumab binds to serum IL-1β. The distribution volume (Vss) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg, 3.2 litres in a SJIA patient of body weight 33 kg and 7.9 litres in a gout patient of body weight 93 kg. The expected accumulation ratio was 1.3-fold, 1.6-fold and 1.1-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks, 4 mg/kg every 4 weeks and 150 mg every 12 weeks respectively (see section DOSAGE REGIMEN AND ADMINISTRATION).

Elimination

The clearance (CL) of canakinumab varied according to body weight. They were estimated to be 0.17 L/day in a CAPS patient of body weight 70 kg, 0.11 L/day in a SJIA patient of body weight 33 kg and 0.23 L/day in a gout patient of body weight 93 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS, SJIA and gouty arthritis patients.

There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender or age-related pharmacokinetic differences were observed after correction for body weight.

Pediatric patients

Peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in pediatric patients 4 years of age and older . The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Based on the population PK modeling analysis in CAPS, the pharmacokinetics of canakinumab in children 2 to <4 years of age were similar to patients 4 years of age and older.

Pharmacokinetic properties are similar in CAPS and SJIA pediatric patients.

In SJIA, exposure parameters (such as AUC and C_{max}) were comparable across age groups from 2 to <20 years following subcutaneous administration of canakinumab 4 mg/kg every 4 weeks.

Geriatric patients (65 years of age or above)

No change in pharmacokinetic parameters based on clearance or volumes of distribution were observed between geriatric patients and adult patients <65 years of age.

CLINICAL STUDIES

CAPS

The efficacy and safety of Ilaris have been demonstrated in patients with varying degrees of disease severity and different CAPS phenotypes (including FCAS/FCU, MWS, and NOMID/CINCA). Only patients with confirmed NLRP3 mutation were included in the pivotal study.

In the Phase I/II study, treatment with Ilaris had a rapid onset of action, with disappearance or clinically significant improvement of symptoms within one day after dosing. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalized rapidly within days of Ilaris injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. a 8-week open-label period (Part I), a 24-week randomized, double-blind, placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). The aim of the study was to assess efficacy, safety, and tolerability of Ilaris (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- **Part I**: A complete clinical and biomarker response to Ilaris (defined as composite of: physician's global assessment on autoinflammatory and on skin disease ≤ minimal and CRP or SAA values <10 mg/L) was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms and patient's assessment of symptoms.
- **Part II**: In the withdrawal period of the pivotal study, the primary endpoint was defined as disease relapse/flare: none (0%) of the patients randomized to Ilaris flared, compared with 81% of the patients randomized to placebo.
- **Part III**: Patients treated with placebo in Part II who flared regained and maintained clinical and serological response following entry into the open-label Ilaris extension.

Table 3 Tabulated summary of efficacy in Phase III trial, pivotal placebo-controlled withdrawal period (Part II)

Phase III trial, pivotal placebo-controlled withdrawal period (part II)			
	Canakinumab n=15	**Placebo n=16**	**p-value**
Primary endpoint (flare)			
Proportion of patients with disease flare in Part II	0 (0%)	13 (81%)	<0.001
Inflammatory markers*			
C-reactive protein mg/l	1.10 (0.40)	19.93 (10.50)	<0.001
Serum amyloid A, mg/l	2.27 (-0.20)	71.09 (14.35)	0.002
*mean (median) change from beginning of Part II			

Two open-label, uncontrolled, long-term phase III studies were performed. One was a safety, tolerability, and efficacy study of canakinumab in patients with CAPS. The total treatment duration ranged from 6 months to 2 years. The other was an open-label study with canakinumab to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks with an extension phase up to 48 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24 including those patients whose dose was increased.

In the pooled efficacy analysis for these two studies, 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Fewer patients aged 2 to <4 years achieved complete response (57.1%) than older pediatric and adult patients. Of the patients who had achieved a complete response, 89.3% maintained response without relapsing.

Experience from individual patients who achieved a complete response following dose escalation to 600 mg (8 mg/kg) every eight weeks have received up-titration doses of maximum 300 mg (4 mg/kg for patients ≥15 kg and ≤40 kg) suggests that a higher dose may be beneficial in patients not achieving complete response or not maintaining complete response with the recommended doses (150 mg or 2 mg/kg for patients ≥15 kg and ≤40 kg). An increased dose was administered more frequently to patients aged 2 to <4 years and patients with NOMID/CINCA symptoms compared with FCAS or MWS.

Pediatric population

The CAPS trials with Ilaris included a total of 69 pediatric patients with an age range from 2 to 17 years. Overall, there were no clinically meaningful differences for the efficacy, safety and tolerability profile of Ilaris in pediatric patients compared to the overall CAPS population (comprised of adult and pediatric patients, N=194) . The majority of pediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., SAA and CRP).

Systemic Juvenile Idiopathic Arthritis

The efficacy of Ilaris for the treatment of active SJIA was assessed in two pivotal phase III studies (G2305 and G2301). Patients enrolled were aged 2 to <20 years (mean age at baseline: 8.5 years) with a confirmed diagnosis of SJIA at least 2 months before enrollment (mean disease duration at baseline: 3.5 years). Patients had active disease defined as ≥2 joints with active arthritis (mean number of active joints at baseline: 15.4), documented spiking, intermittent fever (body temperature >38°C) for at least 1 day within 1 week before study drug administration, and CRP >30 mg/L (normal range <10 mg/L) (mean CRP at baseline: 200.5 mg/L). Patients were allowed to continue their stable dose of methotrexate, corticosteroids, and/or NSAIDs without change, except for tapering of the corticosteroid dose as per study design in Study G2301 (see below).

Study G2305

Study G2305 was a randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short term efficacy of Ilaris in 84 patients randomized to receive a single subcutaneous (s.c.) dose of 4 mg/kg Ilaris or placebo (43 patients received Ilaris and 41 patients received placebo). The primary objective of this study was to demonstrate the superiority of Ilaris versus placebo in the proportion of patients who achieved at least 30% improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion which included both the pediatric ACR core set (ACR30 response) and absence of fever (temperature ≤38°C in the preceding 7 days) at Day 15. Additionally, “inactive disease” (defined as no active arthritis, no fever, no rash, no serositis, no hepatomegaly or lymphadenopathy attributable to SJIA, normal CRP, and physician global assessment indicating no disease activity) was evaluated.

Pediatric ACR responses are defined as the percentage improvement (30%, 50%, 70%, 90%, and 100%) from baseline in 3 of any 6 core outcome variables, with worsening of ≥30% in no more than one of the remaining variables. Core outcome variables included a physician global assessment of disease activity, parent or patient global assessment of wellbeing, number of joints with active arthritis, number of joints with limited range of motion, CRP and functional ability (Childhood Health Assessment Questionnaire - CHAQ).

All primary and secondary endpoints were met. Percentage of patients by pediatric ACR response and inactive disease are presented in Table 4.

Table 4 Pediatric ACR response and disease status at Days 15 and 29

	Day 15		Day 29	
	Ilaris N=43	Placebo N=41	Ilaris N=43	Placebo N=41
ACR30	84%	10%	81%	10%
ACR50	67%	5%	79%	5%
ACR70	61%	2%	67%	2%
ACR90	42%	0%	47%	2%
ACR100	33%	0%	33%	2%
Inactive disease	33%	0%	30%	0%

Treatment difference for all ACR scores was p≤0.0001 and not available for inactive disease.

Ilaris treatment improved components of pediatric ACR core set as compared to placebo at Days 15 and 29 (Table 5). All patients treated with Ilaris had no fever at Day 3 compared to 86.8% of patients treated with placebo (p=0.0098).

Table 5 Median value (median percent change from baseline) at Days 15 and 29 for pediatric ACR core components and pain

Pediatric ACR component	Baseline		Day 15		Day 29	
	Ilaris N=43	Placebo N=41	Ilaris N=43	Placebo N=25	Ilaris N=38*	Placebo N=7
Joints with active arthritis	10	7	2 (-67%)	9 (0%)	1 (-86%)	4 (-32%)
Joints with limited range of motion	8	6	2 (-73%)	8 (0%)	2 (-83%)	2 (-33%)
CRP (mg/L)	141	137	10 (-91%)	99 (5%)	12 (-91%)	81 (-13%)

Pediatric ACR component	Baseline		Day 15		Day 29	
CHAQ disability score	1.63	1.50	0.63 (-68%)	1.63 (-11%)	0.19 (-85%)	1.5 (20%)
Physician global assessment of disease activity VAS (mm)	67	66	20 (-69%)	56 (-5%)	11 (-83%)	28 (-38%)
Parent/patient global assessment of overall wellbeing VAS (mm)	63	61	15 (-73%)	65 (1%)	7 (-91%)	60 (-17%)
Patient pain score VAS (mm)	73	67	8 (-87%)	66 (15%)	7 (-89%)	56 (-12%)

VAS – Visual analog scale (0-100 mm)

A negative value indicates improvement compared to baseline

**Only patients with values at baseline and Days 15 and 29 are represented*

Study G2301

Study G2301 was a randomized, double-blind, placebo-controlled withdrawal study of flare prevention by Ilaris in patients with active SJIA. The study consisted of two major parts with two independent primary endpoints. 177 patients were enrolled in the study and received 4mg/kg s.c. Ilaris every 4 weeks in Part I and either s.c. Ilaris 4mg/kg or placebo every 4 weeks in Part II.

Corticosteroid dose tapering

Part I had an open-label design to assess whether Ilaris allowed successful tapering of corticosteroids in at least 25% of the patients entering the study using a corticosteroid. The primary endpoint of Part I was met. Of the 128 patients who entered the study taking corticosteroids, 57 (45%) successfully tapered the corticosteroid dose ($p<0.0001$) and 42 (33%) discontinued their corticosteroids. Of the 92 patients who attempted corticosteroid tapering, 57 (62%) successfully tapered the corticosteroid dose, 42 (46%) discontinued corticosteroids, 24 (26%) patients still on corticosteroids had the dose reduced to ≤0.2mg/kg/day (prednisone equivalent). Successful corticosteroid dose taperers reduced their mean corticosteroid dose from 0.34 mg/kg/day prednisone equivalent at baseline to 0.05mg/kg/day representing a mean 90% dose reduction. For patients attempting corticosteroid dose reduction who entered with a prednisone equivalent dose of ≥0.5mg/kg/day (N=28), 15 (54%) had their dose reduced by at least 0.3mg/kg which resulted in a prednisone equivalent dose of ≤0.5mg/kg/day, including 7 (25%) who discontinued corticosteroids.

Time to flare

Part II was a withdrawal design to demonstrate that the time to flare was longer with Ilaris than with placebo. The primary endpoint of Part II was met. The probability of experiencing a flare in Part II was statistically lower for the Ilaris treatment group than for the placebo group. The median time to flare was 236 days for the placebo group and could not be determined for the Ilaris group because less than 50% of the patients treated with Ilaris experienced a flare event over the observation period (maximum of > 80 weeks). This corresponded to a statistically significant 64% relative reduced risk for patients in the Ilaris group to experience a flare event as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032).

Pediatric adapted ACR response and pediatric ACR core components

Improvements in the pediatric ACR responses and in each of the pediatric ACR core components observed in Study G2305 (Table 4 and Table 5) were similarly observed during open-label Ilaris treatment in Part I of G2301.

Nearly all (139/141, 98.6%) the patients treated with Ilaris had no fever at Day 3.

In 46 of the 120 patients (38.3%) who entered the study with a low hemoglobin the level had increased to within the normal range at their last visit of Part I.

Health-related and quality of life outcomes in studies G2305 and G2301

Treatment with Ilaris resulted in rapid, sustained, and clinically relevant improvements in patients' quality of life and daily functioning.

In Study G2305, statistically significant improvement from baseline in the CHAQ score for patients treated with Ilaris versus placebo (p=0.0002) was observed, with an estimated difference of the LS means between the treatment groups of -0.69 representing 3.6 times the minimal clinically important difference (MCID) of −0.19. Statistically significant improvements were also observed with Ilaris on the CHQ-PF50 Physical Health score and CHQ-PF50 Psychosocial Health score with an estimated difference in LS means between the Ilaris and placebo treatment groups of 12.1 (p=0.0012) and 7.3 (p=0.0017), respectively.

Similar improvements in the CHAQ score and each of the CHQ-PF50 Health scores observed in Study G2305 were observed during the open-label Ilaris treatment in Part I of Study G2301. The median improvement from baseline to end of Part I for the CHAQ score was -0.88 (-79%), 21.8 (+74%) for the CHQ-PF50 Physical Health score, and 8.2 (+22%) for the CHQ-PF50 Psychosocial Health score.

Initial 12-week treatment data from pooled studies

Data from the first 12 weeks of Ilaris treatment from studies G2305, G2301 and the extension studies were pooled to assess maintenance of efficacy. 12 weeks was chosen to minimize any corticosteroid tapering effects and to exclude the withdrawal part II of study G2301. These data showed similar improvements in the pediatric ACR responses and in each of the pediatric ACR core components to those observed in the individual studies (Table 6). Efficacy data were consistent across age (2-<20 years), gender, disease duration, baseline corticosteroid level, and previous exposure to other therapies including anti-IL-1ra or anti-IL-6r monoclonal antibodies.

Table 6 Adapted ACR pediatric response and median value (median percent change from baseline) in pediatric ACR core components at 12-weeks of Ilaris therapy (pooled data)

Adapted pediatric ACR criteria Ilaris (N=178)		Pediatric ACR core components	Baseline Ilaris (N=178)	12 weeks Ilaris (N=134)*
ACR30	70%	Joints with active arthritis	10	0 (-100%)
ACR50	69%	Joints with limited range of motion	9	1 (-86%)
ACR70	61%	C-reactive protein (mg/L)	158	10 (-94%)
ACR90	49%	CHAQ disability score	1.75	0.25 (-85%)
ACR100	30%	Physician global assessment of disease activity VAS (mm)	70	3 (-96%)
Inactive disease	28%	Parent/patient global	63	5 (-92%)

	assessment of overall wellbeing VAS (mm)

VAS – Visual analog scale (0-100 mm)

A negative value indicates improvement compared to baseline
**Only patients with values at baseline and 12 weeks are represented*

Long-term data

147 patients entered a long-term extension trial and received 4 mg/kg open label Ilaris every 4 weeks. Patients who were strong responders and who did not require a concomitant corticosteroid were allowed to reduce their Ilaris dose to 2 mg/kg every 4 weeks.

At the time of the interim results, 26 patients received at least three consecutive 2 mg/kg doses (median 9 doses) for a median of 224 days of exposure to the reduced dose. All 26 patients had a pediatric ACR 100 response throughout the time the reduced dose was given.

Interim results with a median 49 weeks of follow-up showed that of the 40 patients (27%) who entered the study as non-responders (<Pediatric ACR30), 58% (23/40) were able to regain and maintain a minimum Pediatric ACR30 response. The remaining 107 patients (73%) entered the study as responders (≥Pediatric ACR30) and of these, 94 % (101/107) maintained their responder status and 6% (6/107) lost it (<Pediatric ACR30) at the time of the interim analysis. Seventy six (52%) of the 147 patients who entered the study had inactive disease at the time of the interim analysis. Furthermore, 43% (17/40) of patients who were not successful in tapering their corticosteroid dose in study G2301 were successful in this study including 10/40 (25%) patients who were able to discontinue their corticosteroids.

Immunogenicity

No anaphylactic reactions were observed in patients treated with Ilaris,

Antibodies against ILARIS were observed in approximately 1.5%, 3% and 2 % of the patients treated with ILARIS for CAPS, SJIA and gouty arthritis respectively.. Most of the SJIA clinical studies employed a higher sensitive bridging assay. No neutralizing antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

NON-CLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on cross-reactivity, repeated dose, immunotoxicity, reproductive and juvenile toxicity studies performed with canakinumab or a murine anti-murine IL-1beta antibody.

Since canakinumab binds to marmoset (*C. jacchus*) and human IL-1beta with a similar affinity, the safety of canakinumab has been studied in the marmoset. No undesirable effects of canakinumab were seen following twice weekly administration to marmosets for up to 26 weeks. Plasma concentrations, that are well tolerated in animals are in excess of at least 42-fold (C_{max}) and 78-fold (C_{avg}) the plasma concentrations in pediatric CAPS patients, treated with clinical doses of canakinumab up to 8 mg/kg subcutaneously every eight weeks. Plasma concentrations that are well tolerated in animals exceed at least 62-fold (C_{max}) and 104-fold (C_{avg}) the plasma concentrations in pediatric SJIA patients, treated with up to 4 mg/kg s.c. q 4 weeks canakinumab. In addition, no antibodies to canakinumab were detected in these studies. No non-specific tissue cross-reactivity was demonstrated when canakinumab was applied to normal human tissues.

Formal carcinogenicity studies have not been conducted with canakinumab.

For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

No undesirable effects of a murine anti-murine IL-1beta antibody were seen in a juvenile study in mice. The high dose used in this study was in excess of the maximally effective dose in terms of IL-1beta suppression and activity.

An immunotoxicology study in mice with a murine anti-murine IL-1beta antibody showed that neutralizing IL-1beta has no effects on immune parameters and caused no impairment of immune function in mice.

PHARMACEUTICAL INFORMATION

Incompatibilities

Not Applicable

Special precautions for storage

See folding box.

The unopened vial must be stored at 2°C to 8°C. Do not freeze. Store in the original package in order to protect from light.

Ilaris should not be used after the date marked “EXP” on the pack.

Ilaris should be kept out of the reach and sight of children.

Pack Contents

Powder for solution for injection: packs containing 1 vial of powder.

Instructions for use and handling

Ilaris 150 mg powder for solution for injection is supplied in a single-use vial for individual use. Any unused product or waste material should be disposed of in accordance with local requirements.

Reconstitute the content of Ilaris vial by slowly injecting 1.0 mL water for injections with a 1 mL syringe and an 18 G or 21 G x 2" needle. Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for 5 minutes. Then gently turn the vial upside down and back again ten times. If possible, avoid touching the rubber stopper with your fingers. Allow to stand for about 15 minutes at room temperature . Do not shake. Do not use if particles are present in the solution.

Tap the side of the vial to remove any residual liquid from the stopper. The solution should be free of visible particles and clear to opalescent. The solution should be colorless or may have a slight brownish-yellow tint. If not used within 60 minutes of reconstitution, the solution should be stored in the refrigerator (2°C to 8°C) and used within 24 hours.

Carefully withdraw the required volume depending on the dose to be administered (0.2 mL to 1.0 mL) and subcutaneously inject using a 27 G x 0.5" needle.

Injection into scar-tissue should be avoided as this may result in insufficient exposure to Ilaris.

Special precautions for disposal

Patients or their caregivers should be instructed on the appropriate procedure for disposal of the vials, syringes and needles in accordance with local requirements.

INFORMATION FOR PATIENTS

Instructions for use of Ilaris

Please note that the preparation of the injection takes about 30 minutes.

Injecting Ilaris yourself or to your child

If you are treated for CAPS or SJIA, after proper training in injection technique, you may inject Ilaris yourself or you as a caregiver may inject it to your child (See Section DOSAGE AND ADMINISTRATION).

- You and your doctor should decide together whether or not you will inject Ilaris yourself.
- Your doctor or nurse will show you how to inject yourself.
- Do not try to inject yourself if you have not been properly trained or if you are not sure how to do it.
- Ilaris 150 mg powder for solution for injection (single-use vial) is for individual use only. Any unused product or waste material should be disposed of in accordance with local requirements.
- Never re-use the left-over solution.

Before beginning

- Find a clean, comfortable area.
- Wash your hands with soap and water.
- Check the expiry dates on the vial and syringes. Do not use if the expiry date has passed (last day of the month stamped on the vial).

- Always use new, unopened needles and syringes. Avoid touching the needles and the tops of the vials.

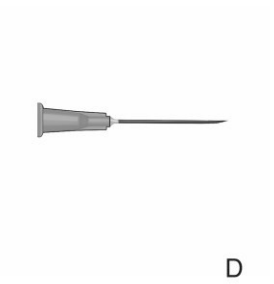
Read these instructions all the way through before beginning.

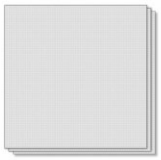
Gather together the necessary items

Included in the pack:

 A	A. One vial of Ilaris powder for solution for injection (keep refrigerated at 2°C to 8°C).

Not included in the pack:

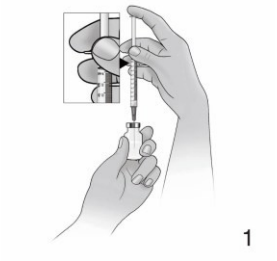
 B	B. One vial of sterile water for injections (“water”) (do not refrigerate).
 C	C. One 1.0 mL syringe.
 D	D. One 18 G x 2” (50 mm) needle for reconstituting the powder (“transfer needle”).

 E	E. One 27 G x 0.5” (13 mm) needle for injecting (“injection needle”).
 F	F. Alcohol swabs.
 G	G. Clean, dry cotton swabs.
 H	H. An adhesive plaster.
 I	I. A proper disposal container for used needles, syringe and vials (sharps container).

Mixing Ilaris

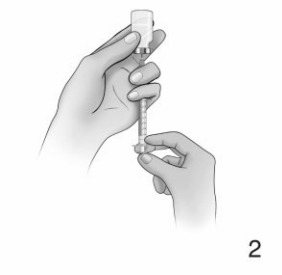
1. Remove the protective caps from vials A and B. Do not touch the vial stoppers. Clean the stoppers with the alcohol swab (F).
2. Open the wrappers containing the syringe (C) and the transfer needle (D) (bigger one) and

attach the needle to the syringe.



1

3. Carefully remove the cap from the transfer needle and set the cap aside. Pull the plunger all the way down to the 1.0 mL mark, filling the syringe with air. Insert the needle into the water vial through the centre of the rubber stopper (Fig. 1).
4. Gently push the plunger all the way down until air is injected into the vial.



2

5. Invert the vial and syringe assembly and bring to eye level (Fig. 2).
6. Make sure the tip of the transfer needle is covered by the water and slowly pull the syringe plunger down to slightly past the 1.0 mL mark. If you see bubbles in the syringe, remove bubbles as instructed by your healthcare provider or pharmacist.
7. Make sure 1.0 mL of water is in the syringe, then withdraw the needle from the vial. (There will be water remaining in the vial).

3

8. Insert the transfer needle through the centre of the stopper of the vial of Ilaris powder (A), taking care not to touch the needle or the stopper. Slowly inject 1.0 mL of water in to the vial containing the Ilaris powder (Fig. 3)
9. Carefully remove the syringe with the transfer needle from the vial and recap the needle as instructed by your healthcare provider or pharmacist.

4a

10. Without touching the rubber stopper, swirl (do not shake) the vial slowly at an angle of about 45 degrees for approximately 1 minute (Fig. 4a). Allow to stand for 5 minutes.
11. Now, gently turn the vial head over tail ten times, again taking care not to touch the rubber stopper (Fig. 4b).
12. Allow to stand for about 15 minutes at room temperature to obtain a clear solution. Do not shake. Do not use if particles are present in the solution.
13. Make sure all of the solution is in the bottom of the vial. If drops remain on the stopper, tap the side of the vial to remove them. The solution should be clear to opalescent and essentially free of visible particles. The solution should be colorless or may have a slight brownish-yellow tint.

4b

If not used within 1 hour of mixing, the solution should be stored in the refrigerator (2 to 8°C) and used within 24 hours.

Preparing the injection

5

14. Clean the rubber stopper of the vial containing the Ilaris solution with a new alcohol swab.
15. Uncap the transfer needle again. Pull the plunger of the syringe all the way down to the 1.0 mL mark, filling the syringe with air. Insert the syringe needle into the vial of Ilaris solution through the centre of the rubber stopper (Fig. 5). Gently push the plunger all the way down until air is injected into the vial. Do not inject air into the medication.
16. **Do not** invert the vial and syringe assembly (Fig. 6a). Insert the needle all the way into the vial until it reaches the bottom edge.

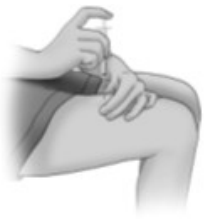
6a

6b

17. Tip the vial to ensure that the required amount of solution can be drawn into the syringe (Fig. 6b). NOTE: The required amount depends on the dose to be administered (0.2 mL to 1.0 mL). Your healthcare provider will instruct you on the right amount for you.
18. Slowly pull the syringe plunger up to the correct mark (0.2 to 1.0 mL), filling the syringe with Ilaris solution. If there are air bubbles in the syringe, remove bubbles as instructed by your healthcare provider. Ensure that the correct amount of solution is in the syringe.
19. Remove the syringe and needle from the vial. (There may be solution remaining in the vial.) Recap the transfer needle as instructed by your healthcare provider or pharmacist. Remove the transfer needle from the syringe. Place the transfer needle in the sharps container (I).

    Open the wrapper containing the injection needle (E) and attach the needle to the syringe. Set the syringe aside.

Giving the injection



7

20. Choose an injection site on the upper arm, upper thigh, abdomen or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Avoid injecting into scar-tissue as this may lead to insufficient exposure to canakinumab. Avoid injecting into a vein.
21. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle.
22. Gently pinch the skin up at the injection site. Hold the syringe at a 90-degree angle and in a single, smooth motion, push the needle straight down completely into the skin (Fig. 7).

8

23. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty (Fig. 8). Release the pinched skin and pull the needle straight out. Dispose of the needle and syringe in the sharps container without recapping or removing the needle.

After the injection

9

24. Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops (Fig. 9). Then apply an adhesive plaster (H).

10

25. Safely dispose of needles and syringe in the sharps container or as directed by your healthcare provider or pharmacist (Fig. 10). Never reuse syringes or needles.
26. Properly dispose of vials containing remaining water and Ilaris solution (if any) as directed by your healthcare provider or pharmacist. Water and solution should not be stored or re-used after injecting. Never recycle or dispose of vials, needles or syringes in the household waste.

Keep the sharps container out of reach of children. Dispose of it as directed by your healthcare provider or pharmacist

Manufacturer:

See folding box.

International Package Leaflet

Information issued: September 2018.SINv1

® = registered trademark

Novartis Pharma AG, Basel, Switzerland