

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of canakinumab*.

After reconstitution, each ml of solution contains 150 mg canakinumab.

* human monoclonal antibody produced in mouse myeloma Sp2/0 cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

The powder is white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Ilaris is indicated for the treatment of 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)

Ilaris is indicated for the treatment of tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS).

Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)

Ilaris is indicated for the treatment of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD).

Familial Mediterranean fever (FMF)

Ilaris is indicated for the treatment of Familial Mediterranean Fever (FMF). Ilaris should be given in combination with colchicine, if appropriate.

Ilaris is also indicated for the treatment of:

Still's disease

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 aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. 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 (see section 5.1).

4.2 Posology and method of administration

For CAPS, TRAPS, HIDS/MKD, FMF and Still's disease, the treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.

For gouty arthritis, the physician should be experienced in the use of biologics and Ilaris should be administered by a healthcare professional.

Posology

CAPS: Adults, adolescents and children aged 2 years and older

The recommended starting dose of canakinumab for CAPS patients is:

Adults, adolescents and children ≥ 4 years of age:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
- 4 mg/kg for patients 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.

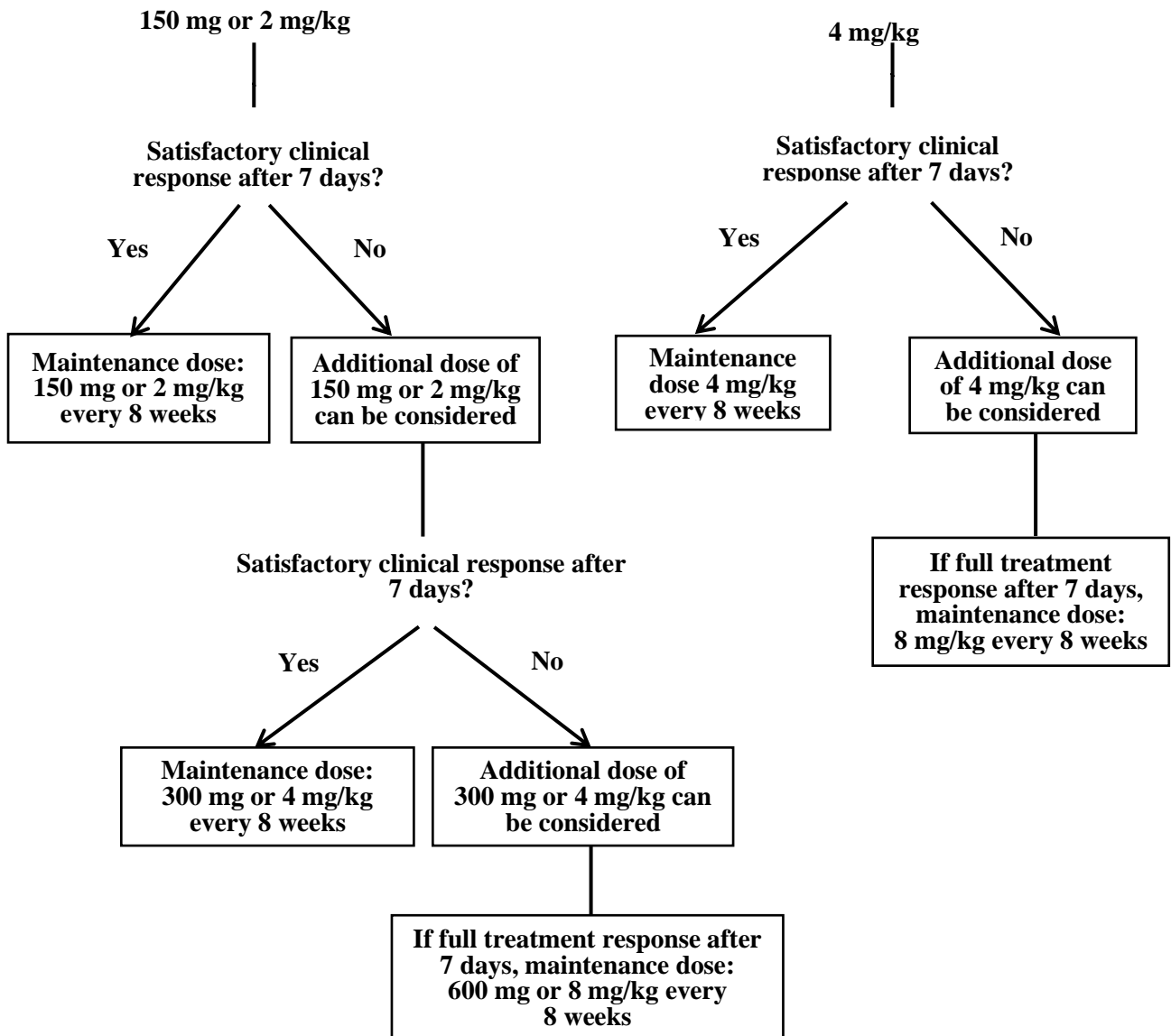
For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 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 canakinumab at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

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

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

CAPS in adults and children ≥ 4 years of age ≥ 15 kg

CAPS in children 2- < 4 years of age or children ≥ 4 years of age ≥ 7.5 kg and < 15 kg



TRAPS, HIDS/MKD and FMF: Adults, adolescents and children aged 2 years and older

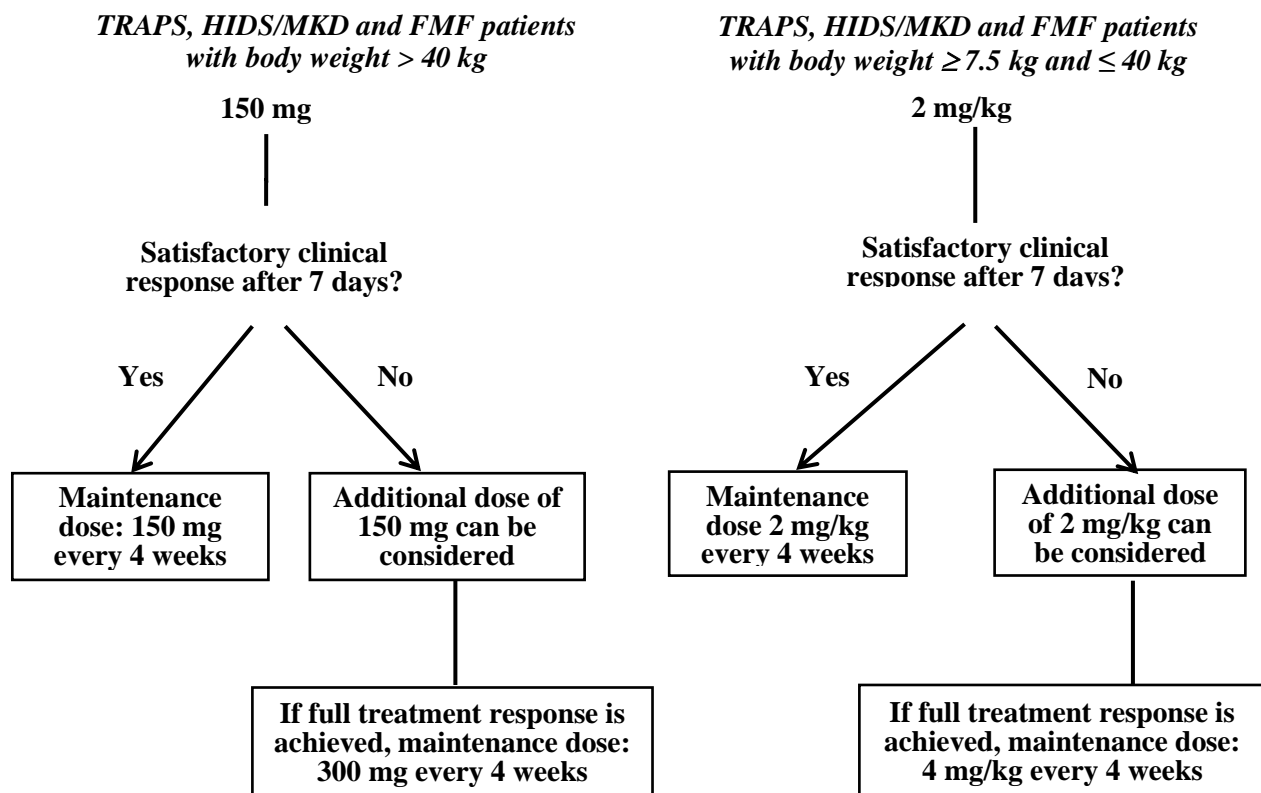
The recommended starting dose of canakinumab in TRAPS, HIDS/MKD and FMF patients is:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 7.5 kg and ≤ 40 kg

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

If a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab 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 (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks should be maintained.

Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.



Still's disease (SJIA and AOSD)

The recommended dose of canakinumab for patients with Still's disease with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.

Gouty arthritis

Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. Canakinumab should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of canakinumab for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, canakinumab should be administered as soon as possible after the onset of a gouty arthritis attack.

Patients who do not respond to initial treatment should not be re-treated with canakinumab. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of canakinumab may be administered (see section 5.2).

Special populations

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 sections 4.8, 5.1 and 5.2 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.

Gouty arthritis

There is no relevant use of canakinumab in the paediatric population in the indication gouty arthritis.

Elderly

No dose adjustment is required.

Hepatic impairment

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

Renal impairment

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

Method of administration

For subcutaneous use.

The following are suitable injection sites: upper thigh, abdomen, upper arm or buttocks. It is recommended to select a different injection site each time the product is injected to avoid soreness. Broken skin and areas which are bruised or covered by a rash should be avoided. Injection into scar tissue should be avoided as this may result in insufficient exposure to canakinumab.

Each vial is for single use in a single patient, for a single dose.

After proper training in the correct injection technique, patients or their caregivers may inject canakinumab if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

Treatment of CAPS, TRAPS, HIDS/MKD, FMF and Still's disease (SJIA and AOSD)

Canakinumab should not be initiated or continued in patients during an active infection requiring medical intervention.

Treatment of gouty arthritis

Canakinumab should not be administered during an active infection.

Concomitant use of canakinumab with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section 4.5).

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

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. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma release assay 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 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. 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.

Neutropenia and leukopenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10⁹/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. 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.

Malignancies

Malignancy events have been reported in patients treated with canakinumab. The risk for the development of malignancies with anti-interleukin (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 2,600 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 4.3).

Hepatic function

Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8).

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 (see section 4.5).

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 (see section 4.5).

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)

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between canakinumab and other medicinal products have not been investigated in formal studies.

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

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as interleukin-1 beta (IL-1 beta). Thus, CYP450 expression may be reversed 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.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of canakinumab treatment, the recommendation is to wait for at least 3 months after the last canakinumab injection and before the next one (see section 4.4).

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

The results of a 56-week, open label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective antibody levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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.

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. 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 canakinumab before childbirth. 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.

Breast-feeding

It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during canakinumab therapy should therefore only be taken after a thorough benefit-risk evaluation.

Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).

Fertility

Formal studies of the potential effect of canakinumab on human fertility have not been conducted. Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Ilaris has minor influence on the ability to drive and use machines. Treatment with Ilaris may result in dizziness/vertigo or asthenia (see section 4.8). Patients who experience such symptoms during Ilaris treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

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.

Hypersensitivity reactions have been reported in patients treated with canakinumab (see sections 4.3 and 4.4).

Opportunistic infections have been reported in patients treated with canakinumab (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency category with the most common first. Frequency categories are defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 list of adverse reactions

MedDRA System Organ Class	Indications: CAPS, TRAPS, HIDS/MKD, FMF, SJIA, gouty arthritis
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 ¹
Uncommon	Gastro-oesophageal reflux disease ²
Skin and subcutaneous tissue disorders	
Very common	Injection site reaction
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia ¹
Common	Musculoskeletal pain ¹ Back pain ²
General disorders and administration site conditions	
Common	Fatigue/asthenia ²
Investigations	
Very common	Creatinine renal clearance decreased ^{1,3} Proteinuria ^{1,4} Leukopenia ^{1,5}
Common	Neutropenia ⁵
Uncommon	Platelet count decreased ⁵
¹ In SJIA ² In gouty arthritis ³ Based on estimated creatinine clearance, most were transient ⁴ Most represented transient trace to 1+ positive urinary protein by dipstick ⁵ See further information below	

Still's Disease (SJIA and AOSD)**SJIA pooled analysis and AOSD**

A total of 445 SJIA patients aged 2 to < 20 years received canakinumab in clinical trials, including 321 patients aged 2 to < 12 years, 88 patients aged 12 to < 16 years, and 36 patients aged 16 to < 20 years. A pooled safety analysis of all SJIA patients showed that in the subset of young adult SJIA patients aged 16 to < 20 years, the safety profile of canakinumab was consistent with what was observed in SJIA patients less than 16 years of age. The safety profile of canakinumab in AOSD patients in a randomised, double blind placebo-controlled study (GDE01T) in 36 adult patients (aged 22 to 70 years) was similar to what was observed in SJIA patients.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients

During clinical trials with canakinumab in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.

Elevations of transaminases have been observed rarely in CAPS patients.

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

In the long-term, open-label studies with dose escalation, events of infections (gastroenteritis, respiratory tract infection, 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 in TRAPS, HIDS/MKD and FMF patients

Neutrophils

Although \geq Grade 2 reductions in neutrophil count occurred in 6.5% of patients (common) and Grade 1 reductions occurred in 9.5% of patients, the reductions are generally transient and neutropenia-associated infection has not been identified as an adverse reaction.

Platelets

Although reductions in platelet count (\geq Grade 2) occurred in 0.6% of patients, bleeding has not been identified as an adverse reaction. Mild and transient Grade 1 reduction in platelets occurred in 15.9% of patients without any associated bleeding adverse events.

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%).

In the overall SJIA programme, transient decreases in absolute neutrophil count (ANC) to less than $1 \times 10^9/l$ were reported in 12 patients (6.0%).

In the overall SJIA programme, 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%).

Laboratory abnormalities in gouty arthritis patients

Haematology

Decreased white blood cell counts (WBC) ≤ 0.8 x lower limit of normal (LLN) were reported in 6.7% of patients treated with canakinumab compared to 1.4% treated with triamcinolone acetonide.

Decreases in absolute neutrophil counts (ANC) to less than $1 \times 10^9/l$ were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts $< 0.5 \times 10^9/l$ were also observed (see section 4.4).

Mild ($<$ LLN and $> 75 \times 10^9/l$) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with canakinumab in the active-controlled clinical studies versus the comparator (7.7%) in gouty arthritis patients.

Uric acid

Increases in uric acid level (0.7 mg/dl at 12 weeks and 0.5 mg/dl at 24 weeks) were observed after canakinumab treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on ULT, increases in uric acid were not observed. Uric acid increases were not observed in clinical trials in non-gouty arthritis populations (see section 5.1).

ALT/AST

Mean and median increases in alanine transaminase (ALT) of 3.0 U/l and 2.0 U/l, respectively, and in aspartate transaminase (AST) of 2.7 U/l and 2.0 U/l, respectively, from baseline to end of study were seen in the canakinumab-treated groups versus the triamcinolone acetonide-treated group(s), however the incidence of clinically significant changes (≥ 3 x the upper limit of normal) was greater for patients treated with triamcinolone acetonide (2.5% for both AST and ALT) compared with canakinumab-treated patients (1.6% for ALT and 0.8% for AST).

Triglycerides

In active-controlled gouty arthritis trials, there was a mean increase in triglycerides of 33.5 mg/dl in canakinumab-treated patients compared with a modest decrease of -3.1 mg/dl with triamcinolone acetonide. The incidence of patients with triglyceride elevations > 5 x upper limit of normal (ULN) was 2.4% with canakinumab and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Long term data from observational study

A total of 243 CAPS patients (85 paediatric patients aged ≥ 2 to ≤ 17 years and 158 adult patients aged ≥ 18 years) were treated with canakinumab in routine clinical practice in a long-term registry study (mean of 3.8 years of canakinumab exposure). The safety profile of canakinumab observed following long-term treatment in this setting was consistent with what has been observed in interventional studies in CAPS patients.

Paediatric population

There were 80 paediatric CAPS patients (2-17 years of age) who received canakinumab in the interventional studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211), including the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract were the most frequently reported infection events.

Additionally, 6 paediatric patients under the age of 2 years were evaluated in a small open-label clinical study. The safety profile of canakinumab appeared similar to that in patients aged 2 years and above.

There were 102 TRAPS, HIDS/MKD and FMF patients (2-17 years of age) who received canakinumab in a 16-week study. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall population.

Elderly population

There is no significant difference in safety profile observed in patients ≥ 65 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC08

Mechanism of action

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

Pharmacodynamic effects

CAPS, TRAPS, HIDS/MKD and FMF

In clinical studies, CAPS, TRAPS, HIDS/MKD and FMF patients who have uncontrolled over-production of IL-1 beta show a rapid and sustained response to therapy with canakinumab, i.e. laboratory parameters such as high C-reactive protein (CRP) and serum amyloid A (SAA), high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

Still's disease (SJIA and AOSD)

Adult-onset Still's disease and systemic juvenile idiopathic arthritis are severe autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1-beta.

Common features of SJIA and AOSD 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 Clinical efficacy and safety).

Gouty arthritis

A gouty arthritis attack is caused by urate (monosodium urate monohydrate) crystals in the joint and surrounding tissue, which trigger resident macrophages to produce IL-1 beta via the "NALP3 inflammasome" complex. Activation of macrophages and concomitant over-production of IL-1 beta results in an acute painful inflammatory response. Other activators of the innate immune system, such as endogenous agonists of toll-like receptors, may contribute to the transcriptional activation of the IL-1 beta gene, initiating a gouty arthritis attack. Following canakinumab treatment, the inflammatory markers CRP or SAA and signs of acute inflammation (e.g. pain, swelling, redness) in the affected joint subside rapidly.

Clinical efficacy and safety

CAPS

The efficacy and safety of canakinumab have been demonstrated in a total of 211 adult and paediatric 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 canakinumab 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 normalised rapidly within days of canakinumab injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. an 8-week open-label period (Part I), a 24-week randomised, 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 canakinumab (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- Part I: A complete clinical and biomarker response to canakinumab (defined as composite of physician's global assessment on autoinflammatory and on skin disease \leq minimal and CRP or SAA values < 10 mg/litre) 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 the proportion of patients with a disease relapse/flare: none (0%) of the patients randomised to canakinumab flared, compared with 81% of the patients randomised 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 canakinumab extension.

Table 2 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 n(%)	Placebo N=16 n(%)	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 paediatric 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 8 weeks 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 to patients with NOMID/CINCA symptoms compared with FCAS or MWS.

A 6-year observational registry study was conducted to provide data on the long-term safety and effectiveness of canakinumab treatment in paediatric and adult CAPS patients in routine clinical practice. The study included 243 CAPS patients (including 85 patients less than 18 years of age). Disease activity was rated as absent or mild/moderate in more than 90% of patients at all post-baseline time points in the study, and median serological markers of inflammation (CRP and SAA) were normal (< 10 mg/litre) at all post-baseline time points. Although approximately 22% of patients receiving canakinumab required dose adjustment, only a small percentage of patients (1.2%) discontinued canakinumab due to lack of therapeutic effect.

Paediatric population

The CAPS interventional trials with canakinumab included a total of 80 paediatric patients with an age range from 2 to 17 years (approximately half of them treated on an mg/kg basis). Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population. The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

A 56-week, open-label study was conducted to assess the efficacy, safety and tolerability of canakinumab in paediatric CAPS patients ≤ 4 years of age. Seventeen patients (including 6 patients under the age of 2 years) were evaluated, using weight-based starting doses of 2-8 mg/kg. The study also evaluated the effect of canakinumab on the development of antibodies to standard childhood vaccines. No differences in safety or efficacy were observed in patients under the age of 2 years compared with patients aged 2 years and above. All patients who received non-live, standard of care childhood vaccinations (N=7) developed protective antibody levels.

TRAPS, HIDS/MKD and FMF

The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD and FMF were demonstrated in a single, pivotal, phase III, 4-part study (N2301) consisting of three separate disease cohorts.

- Part I: Patients in each disease cohort aged 2 years and older entered a 12-week screening period during which they were evaluated for the onset of disease flare.
- Part II: Patients at flare onset were randomised into a 16-week double-blind, placebo-controlled treatment period during which they received either 150 mg canakinumab (2 mg/kg for patients with body weight ≤ 40 kg) subcutaneous (s.c.) or placebo every 4 weeks. Patients > 28 days but < 2 years of age were allowed to enter the study directly into an open-arm of Part II as non-randomised patients (and were excluded from the primary efficacy analysis).
- Part III: Patients who completed 16 weeks of treatment and were classified as responders were re-randomised into a 24-week, double-blind withdrawal period during which they received canakinumab 150 mg (2 mg/kg for patients ≤ 40 kg) s.c. or placebo every 8 weeks.
- Part IV: All Part III patients treated with canakinumab were eligible to enter into a 72-week open-label treatment extension period.

A total of 185 patients aged 28 days and above were enrolled and a total of 181 patients aged 2 years and above were randomised in part II of the study.

The primary efficacy endpoint of the randomised treatment period (Part II) was the proportion of responders within each cohort who had resolution of their index disease flare at day 15 and did not experience a new flare during the remainder of the 16-week treatment period (defined as complete response). Resolution of the index disease flare was defined as having a Physician's Global Assessment (PGA) of Disease Activity score < 2 ("minimal or no disease") and CRP within normal range (≤ 10 mg/l) or reduction $\geq 70\%$ from baseline. A new flare was defined as a PGA score ≥ 2 ("mild, moderate, or severe disease") and CRP ≥ 30 mg/l. Secondary endpoints, all based on week 16 results (end of Part II), included the proportion of patients who achieved a PGA score of < 2, the proportion of patients with serological remission (defined as CRP ≤ 10 mg/l), and the proportion of patients with a normalised SAA level (defined as SAA ≤ 10 mg/l).

For the primary efficacy endpoint, canakinumab was superior to placebo for all three disease cohorts. Canakinumab also demonstrated superior efficacy compared to placebo on the secondary endpoints of PGA < 2 and CRP ≤ 10 mg/l in all three cohorts. Higher proportions of patients had normalised SAA (≤ 10 mg/l) at week 16 with canakinumab treatment compared to placebo in all three cohorts, with a statistically significant difference observed in TRAPS patients (see Table 3 with study results below).

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

Phase III trial, pivotal, randomised placebo-controlled treatment period (Part II)			
	Canakinumab n/N (%)	Placebo n/N (%)	p-value
Primary endpoint (disease flare) - Proportion of patients who had index disease flare resolution at day 15 and did not experience a new flare during the remainder of the 16-week treatment period			
FMF	19/31 (61.29)	2/32 (6.25)	< 0.0001*
HIDS/MKD	13/37 (35.14)	2/35 (5.71)	0.0020*
TRAPS	10/22 (45.45)	2/24 (8.33)	0.0050*
Secondary endpoints (disease and inflammatory markers)			
Physician Global Assessment < 2			
FMF	20/31 (64.52)	3/32 (9.38)	< 0.0001**
HIDS/MKD	17/37 (45.95)	2/35 (5.71)	0.0006**
TRAPS	10/22 (45.45)	1/24 (4.17)	0.0028**
C-reactive protein ≤ 10 mg/l			
FMF	21/31 (67.74)	2/32 (6.25)	< 0.0001**
HIDS/MKD	15/37 (40.54)	2/35 (5.71)	0.0010**
TRAPS	8/22 (36.36)	2/24 (8.33)	0.0149**
Serum amyloid A ≤ 10 mg/l			
FMF	8/31 (25.81)	0/32 (0.00)	0.0286
HIDS/MKD	5/37 (13.51)	1/35 (2.86)	0.0778
TRAPS	6/22 (27.27)	0/24 (0.00)	0.0235**
n=number of responders; N=number of evaluable patients			
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test			
** Indicates statistical significance (one-sided) at the 0.025 level based on the logistic regression model with treatment group and baseline PGA, CRP or SAA respectively, as explanatory variables for each cohort			

Up-titration

In Part II of the study, patients treated with canakinumab who had persistent disease activity received an additional dose of 150 mg (or 2 mg/kg for patients ≤ 40 kg) within the first month. This additional dose could be provided as early as 7 days after the first treatment dose. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients ≤ 40 kg) every 4 weeks.

In an exploratory analysis of the primary endpoint, it was observed that in patients with an inadequate response after the first dose, an up-titration within the first month to a dose of 300 mg (or 4 mg/kg) every 4 weeks further improved flare control, reduced disease activity and normalised CRP and SAA levels.

Paediatric patients:

Two non-randomised HIDS/MKD patients aged > 28 days but < 2 years were included in the study and received canakinumab. One patient had resolution of index flare by day 15 after receiving one single dose of canakinumab 2 mg/kg, but discontinued treatment after this first dose due to serious adverse events (pancytopenia and hepatic failure). This patient presented at study entry with a history of immune thrombocytopenic purpura and an active medical condition of abnormal hepatic function. The second patient received a starting dose of canakinumab 2 mg/kg and an add-on dose of 2 mg/kg at week 3, and was up-titrated at week 5 to receive a dose of 4 mg/kg administered every 4 weeks until the end of Part II of the study. Resolution of disease flare was achieved by week 5 and the patient had not experienced any new flare at the end of Part II of the study (week 16).

Still's disease (SJIA and AOSD)

SJIA

The efficacy of canakinumab 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 of 8.5 years and mean disease duration of 3.5 years at baseline) and had active disease defined as ≥ 2 joints with active arthritis, fever and elevated CRP.

Study G2305

Study G2305 was a randomised, double-blind, placebo-controlled, 4-week study assessing the short-term efficacy of canakinumab in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) canakinumab or placebo. The primary objective was the proportion of patients at day 15 who achieved a minimum 30% improvement in the paediatric American College of Rheumatology (ACR) response criterion adapted to include absence of fever. Canakinumab treatment improved all paediatric ACR response scores as compared to placebo at days 15 and 29 (Table 4).

Table 4 Paediatric ACR response and disease status at days 15 and 29

	Day 15		Day 29	
	Canakinumab N=43	Placebo N=41	Canakinumab 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 significant ($p \leq 0.0001$)				

Results for the components of the adapted paediatric ACR which included systemic and arthritic components, were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were -67% and -73% for canakinumab (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for canakinumab (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among canakinumab treated patients was consistent at day 29.

Study G2301

Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by canakinumab. The study consisted of two parts with two independent primary endpoints (successful steroid taper and time to flare). In Part I (open label) 177 patients were enrolled and received 4 mg/kg (up to 300 mg) canakinumab administered every 4 weeks for up to 32 weeks. Patients in Part II (double-blind) received either canakinumab 4 mg/kg or placebo every 4 weeks until 37 flare events occurred.

Corticosteroid dose tapering:

Of the total 128 patients who entered Part I taking corticosteroids, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to flare:

Patients taking canakinumab in Part II had a 64% reduced risk of a flare event as compared to the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). Sixty-three of the 100 patients entering Part II, whether assigned to placebo or canakinumab, did not experience a flare over the observation period (up to a maximum of 80 weeks).

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

Treatment with canakinumab resulted in clinically relevant improvements in patients' physical function and quality of life. In study G2305, the Childhood Health Assessment Questionnaire Least Squares means improvement was 0.69 for canakinumab vs placebo representing 3.6 times the minimal clinically important difference of 0.19 (p=0.0002). The median improvement from baseline to end of Part I of study G2301 was 0.88 (79%). Statistically significant improvements in the Child Health Questionnaire-PF50 scores were reported for canakinumab vs placebo in study G2305 (physical p=0.0012; psychosocial well-being p=0.0017).

Pooled efficacy analysis

Data from the first 12 weeks of canakinumab treatment from studies G2305, G2301 and the extension study were pooled to assess maintenance of efficacy. These data showed similar improvements from baseline to week 12 in the adapted paediatric ACR responses and its components to those observed in the placebo controlled study (G2305). At week 12, the adapted paediatric ACR30, 50, 70, 90 and 100 responses were: 70%, 69%, 61%, 49% and 30%, respectively and 28% of patients had inactive disease (N=178).

Although limited, evidence from the clinical trials suggests that patients not responding to tocilizumab or anakinra may respond to canakinumab.

Study G2301E1

The efficacy observed in the studies G2305 and G2301 was maintained in the open-label long-term extension study G2301E1. Of the 270 SJIA patients in the study, 147 patients had received treatment with canakinumab in studies G2305 or G2301 (Cohort I), and 123 patients were canakinumab-naïve patients (Cohort II). Patients in Cohort I were treated for a median duration of 3.2 years (up to 5.2 years), and patients in Cohort II were treated for a median duration of 1.8 years (up to 2.8 years). In the extension study, all patients received canakinumab 4 mg/kg (up to maximum 300 mg) every 4 weeks. In both cohorts, patients who were well-controlled responders (retrospectively defined as adapted paediatric ACR \geq 90) and who did not require a concomitant corticosteroid were permitted to reduce their canakinumab dose to 2 mg/kg every 4 weeks (62/270; 23%).

Study G2306

Study G2306 was an open-label study to assess maintenance of treatment response with canakinumab dose reduction (2 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 8 weeks) in SJIA patients who were receiving canakinumab 4 mg/kg every 4 weeks. Seventy five patients aged 2 to 22 years who maintained inactive disease status for at least 6 consecutive months (clinical remission) with canakinumab monotherapy, including patients who were able to maintain inactive disease status with discontinuation of concomitant corticosteroid and/or methotrexate use for at least 4 weeks, were randomised to receive canakinumab 2 mg/kg every 4 weeks (N=38) or canakinumab 4 mg/kg every 8 weeks (N=37). After 24 weeks, 71% (27/38) of patients who received the reduced dose (2 mg/kg every 4 weeks) and 84% (31/37) of patients who received the prolonged dosing interval (4 mg/kg every 8 weeks) were able to maintain inactive disease status for 6 months. Of the patients in clinical remission who continued with further dose reduction (1 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 12 weeks), 93% (26/28) and 91% (30/33) of patients, respectively, were able to maintain inactive disease status for 6 months. Patients who maintained inactive disease status for 6 additional months at this lowest dose regimen were allowed to discontinue canakinumab. Overall, 33% (25/75) of patients randomised to dose reduction or dose interval prolongation arms were able to discontinue treatment with canakinumab and maintain inactive disease status for 6 months. The rate of adverse events in both treatment arms was similar to the rate seen in patients treated with canakinumab 4 mg/kg every 4 weeks.

AOSD

The efficacy of canakinumab 4 mg/kg (up to maximum 300 mg) administered every 4 weeks in AOSD patients in a randomised, double-blind placebo-controlled study in 36 patients (22 to 70 years old) was comparable to that observed in SJIA patients. In study GDE01T, a higher proportion of patients (12/18, 66.7%) in the canakinumab group than in the placebo group (7/17, 41.2%) demonstrated an improvement from baseline in Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28-ESR) of > 1.2 at week 12, which failed to reach statistical significance (odds ratio 2.86, treatment difference [%] 25.49 [95% CI: 9.43, 55.80]). By week 4, 7 of 18 patients (38.9%) treated with canakinumab had already achieved DAS28-ESR remission versus 2 of 17 patients (11.8%) on placebo. These data are consistent with the results of a pooled efficacy analysis of 418 SJIA patients which showed that the efficacy of canakinumab in a subset of SJIA patients aged 16 to < 20 years (n=34) was consistent with the efficacy observed in patients less than 16 years of age (n=384).

Gouty arthritis

The efficacy of canakinumab for the treatment of acute gouty arthritis attacks was demonstrated in two multicentre, randomised, double-blind, active-controlled studies in patients with frequent gouty arthritis (≥ 3 attacks in the previous 12 months) unable to use NSAIDs or colchicine (due to contraindication, intolerance or lack of efficacy). The studies were 12 weeks followed by 12-week double-blind extension. A total of 225 patients were treated with subcutaneous canakinumab 150 mg and 229 patients were treated with intramuscular triamcinolone acetonide (TA) 40 mg at study entry, and when experiencing a new attack thereafter. The mean number of gouty arthritis attacks in the previous 12 months was 6.5. Over 85% of patients had comorbidity, including hypertension (60%), diabetes (15%), ischaemic heart disease (12%), and stage ≥ 3 chronic kidney disease (25%). Approximately one-third of the patients enrolled (76 [33.8%] in the canakinumab group and 84 [36.7%] in the triamcinolone acetonide group) had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. Concomitant treatment with ULTs was reported by 42% of patients at entry.

The co-primary endpoints were: (i) gouty arthritis pain intensity (visual analogue scale, VAS) at 72 hours post-dose, and (ii) time to first new gouty arthritis attack.

For the overall study population, pain intensity was statistically significantly lower for canakinumab 150 mg compared with triamcinolone acetonide at 72 hours. Canakinumab also reduced the risk of subsequent attacks (see Table 5).

Efficacy results in a subgroup of patients unable to use both NSAIDs and colchicine and who were on ULT, failed ULT or had a contraindication to ULT (N=101) were consistent with the overall study population with a statistically significant difference compared to triamcinolone acetonide in pain intensity at 72 hours (-10.2 mm, p=0.0208) and in reduction of risk of subsequent attacks (Hazard ratio 0.39, p=0.0047 at 24 weeks).

Efficacy results for a more stringent subgroup limited to current users of ULT (N=62) are presented in Table 5. Treatment with canakinumab induced a reduction of pain and reduced the risk of subsequent attacks in patients using ULT and unable to use both NSAIDs and colchicine, although the observed treatment difference compared to triamcinolone acetonide was less pronounced than with the overall study population.

Table 5 Efficacy for the overall study population and in a subgroup of patients currently using ULT and unable to use both NSAIDs and colchicine

Efficacy endpoint	Overall study population; N=454	Unable to use both NSAIDs and colchicine; on ULT N=62
Treatment of gouty arthritis attacks as measured by pain intensity (VAS) at 72 h		
Least Squares mean estimated difference to triamcinolone acetonide	-10.7	-3.8
CI	(-15.4, -6.0)	(-16.7, 9.1)
p-value, 1-sided	p < 0.0001*	p=0.2798
Risk reduction of subsequent gouty arthritis attacks as measured by time to first new flare (24 weeks)		
Hazard ratio to triamcinolone acetonide	0.44	0.71
CI	(0.32, 0.60)	(0.29, 1.77)
p-value, 1-sided	p < 0.0001*	p=0.2337

* Denotes significant p-value ≤ 0.025

Safety results showed an increased incidence of adverse events for canakinumab compared to triamcinolone acetonide, with 66% vs 53% of patients reporting any adverse event and 20% vs 10% of patients reporting an infection adverse event over 24 weeks.

Elderly population

Overall, the efficacy, safety and tolerability profile of canakinumab in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)

In clinical studies, canakinumab has been safely administered with ULT. In the overall study population, patients on ULT had a less pronounced treatment difference in both pain reduction and reduction in the risk of subsequent gouty arthritis attacks compared to patients not on ULT.

Immunogenicity

Antibodies against canakinumab were observed in approximately 1.5%, 3% and 2% of the patients treated with canakinumab for CAPS, SJIA and gouty arthritis, respectively. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

There were no antibodies against canakinumab observed in TRAPS, HIDS/MKD and FMF patients treated with doses of 150 mg and 300 mg over 16 weeks of treatment.

Paediatric population

The Marketing Authorisation Holder has completed four Paediatric Investigation Plans for canakinumab (for CAPS, SJIA, FMF – HIDS/MKD and TRAPS respectively). This product information has been updated to include the results of studies with canakinumab in the paediatric population.

The European Medicines Agency has waived the obligation to submit the results of studies with canakinumab in all subsets of the paediatric population in gouty arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

CAPS

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. Mean values for C_{max} and AUC_{inf} after a single subcutaneous dose of 150 mg in a typical adult CAPS patient (70 kg) were 15.9 $\mu\text{g/ml}$ and 708 $\mu\text{g}\cdot\text{d/ml}$. The absolute bioavailability of subcutaneously administered 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. Predicted steady-state exposure values ($C_{min,ss}$, $C_{max,ss}$, $AUC_{ss,8w}$) after 150 mg subcutaneous administration (or 2 mg/kg, respectively) every 8 weeks were slightly higher in the weight category 40-70 kg (6.6 $\mu\text{g/ml}$, 24.3 $\mu\text{g/ml}$, 767 $\mu\text{g}\cdot\text{d/ml}$) compared to the weight categories < 40 kg (4.0 $\mu\text{g/ml}$, 19.9 $\mu\text{g/ml}$, 566 $\mu\text{g}\cdot\text{d/ml}$) and > 70 kg (4.6 $\mu\text{g/ml}$, 17.8 $\mu\text{g/ml}$, 545 $\mu\text{g}\cdot\text{d/ml}$). The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks.

Distribution

Canakinumab binds to serum IL-1 beta. The distribution volume (V_{ss}) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg.

Elimination

The apparent clearance (CL/F) of canakinumab increases with body weight. It was estimated to be 0.17 l/d in a CAPS patient of body weight 70 kg and 0.11 l/d in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS and SJIA 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.

TRAPS, HIDS/MKD and FMF

Bioavailability in TRAPS, HIDS/MKD and FMF patients has not been determined independently. Apparent clearance (CL/F) in the TRAPS, HIDS/MKD and FMF population at body weight of 55 kg (0.14 l/d) was comparable to CAPS population at body weight of 70 kg (0.17 l/d). The apparent volume of distribution (V/F) was 4.96 l at body weight of 55 kg.

After repeated subcutaneous administration of 150 mg every 4 weeks, canakinumab minimal concentration at week 16 (C_{min}) was estimated to be $15.4 \pm 6.6 \mu\text{g/ml}$. The estimated steady state AUC_{tau} was $636.7 \pm 260.2 \mu\text{g}\cdot\text{d/ml}$.

Still's disease (SJIA and AOSD)

Bioavailability in SJIA patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the SJIA and CAPS population (0.004 l/d per kg). The apparent volume of distribution per kg (V/F per kg) was 0.14 l/kg. Sparse pharmacokinetics (PK) data in AOSD patients suggest similar PK of canakinumab as compared to SJIA and other patient populations.

After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. The overall predicted mean (\pm SD) for $C_{\min,ss}$, $C_{\max,ss}$ and AUC_{ss4w} were 14.7 ± 8.8 μ g/ml, 36.5 ± 14.9 μ g/ml and 696.1 ± 326.5 μ g*d/ml, respectively.

The AUC_{ss4w} in each age group was 692, 615, 707 and 742 μ g*d/ml for 2-3, 4-5, 6-11, and 12-19 years old, respectively. When stratified by weight, a lower (30-40%) median of exposure for $C_{\min,ss}$ (11.4 vs 19 μ g/ml) and AUC_{ss} (594 vs 880 μ g*d/ml) for the lower bodyweight category (≤ 40 kg) vs the higher bodyweight category (> 40 kg) was observed.

Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Gouty arthritis population

Bioavailability in gouty arthritis patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the gouty arthritis and CAPS population (0.004 l/d/kg). Mean exposure in a typical gouty arthritis patient (93 kg) after a single subcutaneous 150 mg dose (C_{\max} : 10.8 μ g/ml and AUC_{inf} : 495 μ g*d/ml) was lower than in a typical 70 kg CAPS patient (15.9 μ g/ml and 708 μ g*d/ml). This is consistent with the observed increase in CL/F with body weight.

The expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.

Paediatric population

Peak concentrations of canakinumab occurred between 2 to 7 days (T_{\max}) following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in paediatric 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 pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in children aged 2 to < 4 years were similar to those in patients 4 years of age and older. Subcutaneous absorption rate was estimated to decrease with age and appeared to be fastest in the youngest patients. Accordingly, T_{\max} was shorter (3.6 days) in younger SJIA patients (2-3 years) compared to older SJIA patients (12-19 years; T_{\max} 6 days). Bioavailability (AUC_{ss}) was not affected.

An additional pharmacokinetics analysis showed that the pharmacokinetics of canakinumab in 6 paediatric CAPS patients under the age of 2 years were similar to the pharmacokinetics in paediatric patients 2-4 years of age. Based on the population pharmacokinetic modelling analysis, the expected exposures after a dose of 2 mg/kg were comparable across the CAPS paediatric age groups, but were approximately 40% lower in paediatric patients of very low body weight (e.g. 10 kg) than in adult patients (150 mg dose). This is consistent with the observations of higher exposure in higher body weight groups in CAPS patients.

In TRAPS, HIDS/MKD and FMF, exposure parameters (trough concentrations) were comparable across age groups from 2 to < 20 years old following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

Pharmacokinetic properties are similar in CAPS, TRAPS, HIDS/MKD, FMF and SJIA paediatric populations.

Elderly population

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of cross-reactivity, repeated dose toxicity, immunotoxicity, toxicity to reproduction and development.

Formal carcinogenicity studies have not been conducted with canakinumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution for injection in a vial (type I glass) with a stopper (coated chlorobutyl rubber) and flip-off cap (aluminium).

Packs containing 1 vial or multipacks containing 4 (4x1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ilaris 150 mg powder for solution for injection is supplied in a single-use vial for individual use.

Instructions for reconstitution

Using aseptic technique, reconstitute each vial of canakinumab at room temperature (typically 15°C to 25°C) by slowly injecting 1 ml water for injections with a 1 ml syringe and an 18 G x 2 inch (50 mm) needle. Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for about 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 to obtain a clear to opalescent solution. 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 colourless or may have a slight brownish-yellow tint. If the solution has a distinctly brown discolouration it should not be used. If not used immediately after reconstitution, the solution should be kept at 2°C to 8°C and used within 24 hours.

Instructions for administration

Carefully withdraw the required volume depending on the dose to be administered (0.1 ml to 1 ml) and subcutaneously inject using a 27 G x 0.5 inch (13 mm) needle.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009

Date of latest renewal: 06 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of canakinumab*.

Each ml of solution contains 150 mg canakinumab.

* human monoclonal antibody produced in mouse myeloma Sp2/0 cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is clear to opalescent and colourless to slightly brownish yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Ilaris is indicated for the treatment of 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)

Ilaris is indicated for the treatment of tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS).

Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)

Ilaris is indicated for the treatment of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD).

Familial Mediterranean fever (FMF)

Ilaris is indicated for the treatment of Familial Mediterranean Fever (FMF). Ilaris should be given in combination with colchicine, if appropriate.

Ilaris is also indicated for the treatment of:

Still's disease

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 aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. 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 (see section 5.1).

4.2 Posology and method of administration

For CAPS, TRAPS, HIDS/MKD, FMF and Still's disease, the treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.

For gouty arthritis, the physician should be experienced in the use of biologics and Ilaris should be administered by a healthcare professional.

Posology

CAPS: Adults, adolescents and children aged 2 years and older

The recommended starting dose of canakinumab for CAPS patients is:

Adults, adolescents and children ≥ 4 years of age:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
- 4 mg/kg for patients 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.

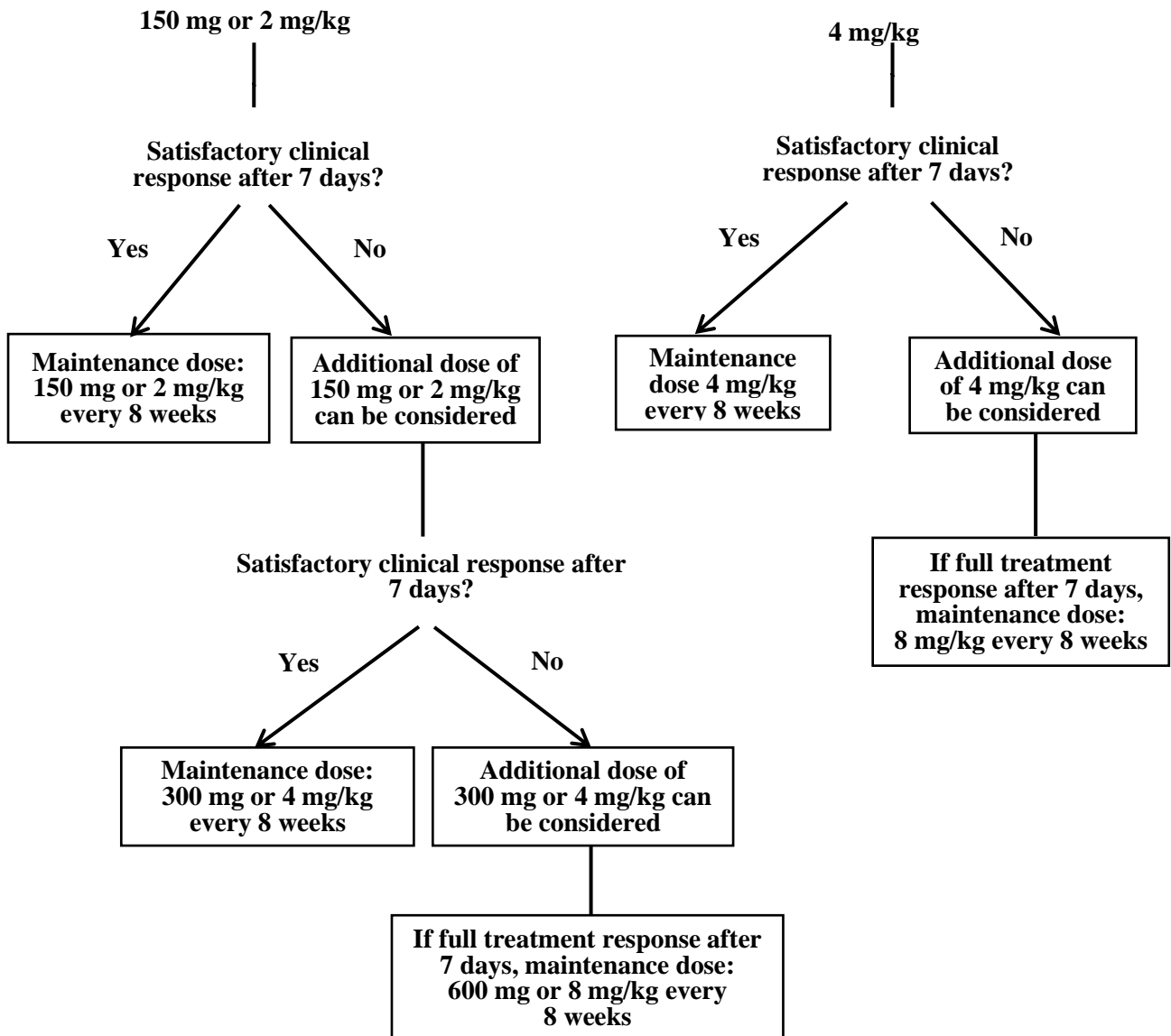
For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 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 canakinumab at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

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

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

CAPS in adults and children ≥ 4 years of age ≥ 15 kg

CAPS in children 2- < 4 years of age or children ≥ 4 years of age ≥ 7.5 kg and < 15 kg



TRAPS, HIDS/MKD and FMF: Adults, adolescents and children aged 2 years and older

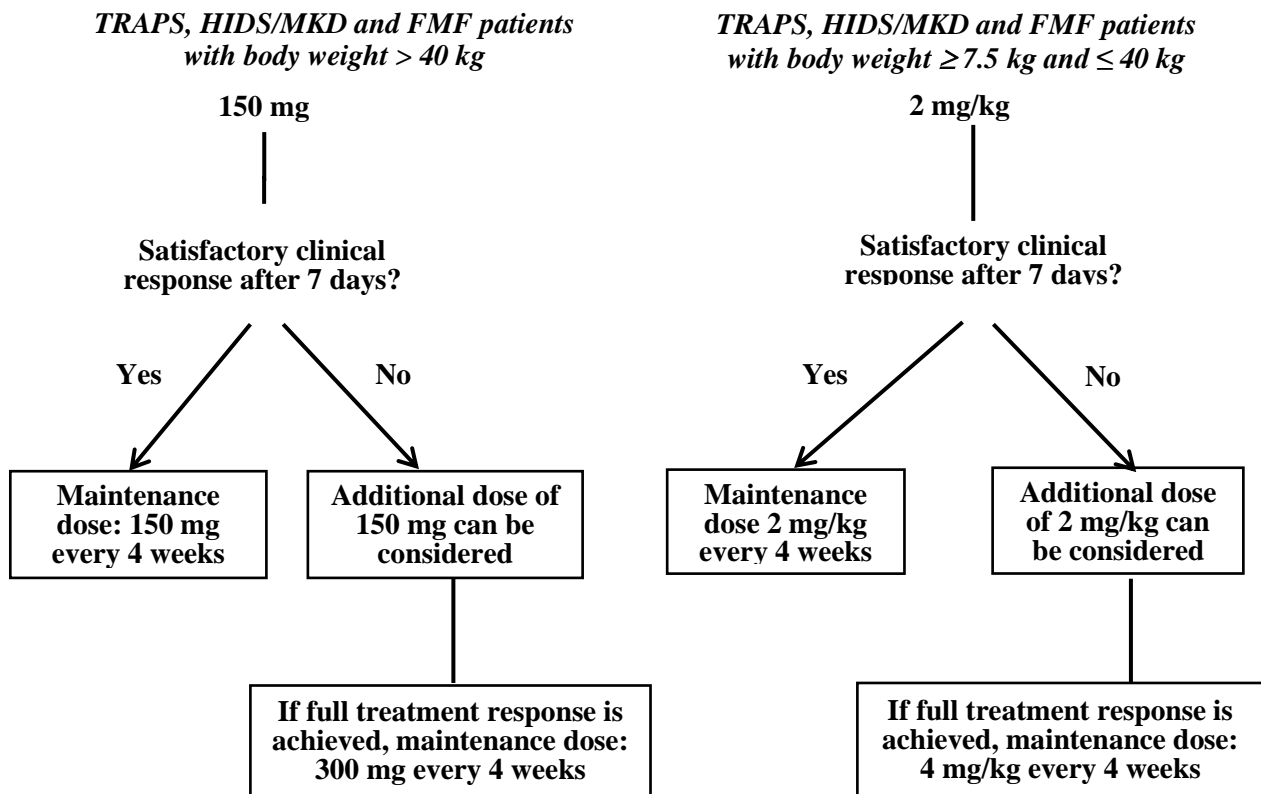
The recommended starting dose of canakinumab in TRAPS, HIDS/MKD and FMF patients is:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 7.5 kg and ≤ 40 kg

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

If a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab 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 (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks should be maintained.

Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.



Still's disease (SJIA and AOSD)

The recommended dose of canakinumab for patients with Still's disease with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.

Gouty arthritis

Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. Canakinumab should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of canakinumab for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, canakinumab should be administered as soon as possible after the onset of a gouty arthritis attack.

Patients who do not respond to initial treatment should not be re-treated with canakinumab. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of canakinumab may be administered (see section 5.2).

Special populations

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 sections 4.8, 5.1 and 5.2 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.

Gouty arthritis

There is no relevant use of canakinumab in the paediatric population in the indication gouty arthritis.

Elderly

No dose adjustment is required.

Hepatic impairment

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

Renal impairment

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

Method of administration

For subcutaneous use.

The following are suitable injection sites: upper thigh, abdomen, upper arm or buttocks. It is recommended to select a different injection site each time the product is injected to avoid soreness. Broken skin and areas which are bruised or covered by a rash should be avoided. Injection into scar tissue should be avoided as this may result in insufficient exposure to canakinumab.

Each vial is for single use in a single patient, for a single dose.

After proper training in the correct injection technique, patients or their caregivers may inject canakinumab if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

Treatment of CAPS, TRAPS, HIDS/MKD, FMF and Still's disease (SJIA and AOSD)

Canakinumab should not be initiated or continued in patients during an active infection requiring medical intervention.

Treatment of gouty arthritis

Canakinumab should not be administered during an active infection.

Concomitant use of canakinumab with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section 4.5).

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

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. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma release assay 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 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. 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.

Neutropenia and leukopenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10⁹/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. 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.

Malignancies

Malignancy events have been reported in patients treated with canakinumab. The risk for the development of malignancies with anti-interleukin (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 2,600 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 4.3).

Hepatic function

Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8).

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 (see section 4.5).

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 (see section 4.5).

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)

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between canakinumab and other medicinal products have not been investigated in formal studies.

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

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as interleukin-1 beta (IL-1 beta). Thus, CYP450 expression may be reversed 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.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of canakinumab treatment, the recommendation is to wait for at least 3 months after the last canakinumab injection and before the next one (see section 4.4).

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

The results of a 56-week, open label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective antibody levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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.

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. 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 canakinumab before childbirth. 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.

Breast-feeding

It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during canakinumab therapy should therefore only be taken after a thorough benefit-risk evaluation.

Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).

Fertility

Formal studies of the potential effect of canakinumab on human fertility have not been conducted. Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Ilaris has minor influence on the ability to drive and use machines. Treatment with Ilaris may result in dizziness/vertigo or asthenia (see section 4.8). Patients who experience such symptoms during Ilaris treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

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.

Hypersensitivity reactions have been reported in patients treated with canakinumab (see sections 4.3 and 4.4).

Opportunistic infections have been reported in patients treated with canakinumab (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency category with the most common first. Frequency categories are defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 list of adverse reactions

MedDRA System Organ Class	Indications: CAPS, TRAPS, HIDS/MKD, FMF, SJIA, gouty arthritis
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 ¹
Uncommon	Gastro-oesophageal reflux disease ²
Skin and subcutaneous tissue disorders	
Very common	Injection site reaction
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia ¹
Common	Musculoskeletal pain ¹ Back pain ²
General disorders and administration site conditions	
Common	Fatigue/asthenia ²
Investigations	
Very common	Creatinine renal clearance decreased ^{1,3} Proteinuria ^{1,4} Leukopenia ^{1,5}
Common	Neutropenia ⁵
Uncommon	Platelet count decreased ⁵
¹ In SJIA ² In gouty arthritis ³ Based on estimated creatinine clearance, most were transient ⁴ Most represented transient trace to 1+ positive urinary protein by dipstick ⁵ See further information below	

Still's Disease (SJIA and AOSD)**SJIA pooled analysis and AOSD**

A total of 445 SJIA patients aged 2 to < 20 years received canakinumab in clinical trials, including 321 patients aged 2 to < 12 years, 88 patients aged 12 to < 16 years, and 36 patients aged 16 to < 20 years. A pooled safety analysis of all SJIA patients showed that in the subset of young adult SJIA patients aged 16 to < 20 years, the safety profile of canakinumab was consistent with what was observed in SJIA patients less than 16 years of age. The safety profile of canakinumab in AOSD patients in a randomised, double blind placebo-controlled study (GDE01T) in 36 adult patients (aged 22 to 70 years) was similar to what was observed in SJIA patients.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients

During clinical trials with canakinumab in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.

Elevations of transaminases have been observed rarely in CAPS patients.

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

In the long-term, open-label studies with dose escalation, events of infections (gastroenteritis, respiratory tract infection, 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 in TRAPS, HIDS/MKD and FMF patients

Neutrophils

Although \geq Grade 2 reductions in neutrophil count occurred in 6.5% of patients (common) and Grade 1 reductions occurred in 9.5% of patients, the reductions are generally transient and neutropenia-associated infection has not been identified as an adverse reaction.

Platelets

Although reductions in platelet count (\geq Grade 2) occurred in 0.6% of patients, bleeding has not been identified as an adverse reaction. Mild and transient Grade 1 reduction in platelets occurred in 15.9% of patients without any associated bleeding adverse events.

Laboratory abnormalities in SJIA patients

Haematology

In the overall SJIA programme, transient decreased white blood cell (WBC) counts $\leq 0.8 \times$ LLN were reported in 33 patients (16.5%).

In the overall SJIA programme, transient decreases in absolute neutrophil count (ANC) to less than $1 \times 10^9/l$ were reported in 12 patients (6.0%).

In the overall SJIA programme, 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 $> 3 \times$ upper limit of normal (ULN) were reported in 19 patients (9.5%).

Laboratory abnormalities in gouty arthritis patients

Haematology

Decreased white blood cell counts (WBC) $\leq 0.8 \times$ lower limit of normal (LLN) were reported in 6.7% of patients treated with canakinumab compared to 1.4% treated with triamcinolone acetonide.

Decreases in absolute neutrophil counts (ANC) to less than $1 \times 10^9/l$ were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts $< 0.5 \times 10^9/l$ were also observed (see section 4.4).

Mild ($<$ LLN and $> 75 \times 10^9/l$) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with canakinumab in the active-controlled clinical studies versus the comparator (7.7%) in gouty arthritis patients.

Uric acid

Increases in uric acid level (0.7 mg/dl at 12 weeks and 0.5 mg/dl at 24 weeks) were observed after canakinumab treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on ULT, increases in uric acid were not observed. Uric acid increases were not observed in clinical trials in non-gouty arthritis populations (see section 5.1).

ALT/AST

Mean and median increases in alanine transaminase (ALT) of 3.0 U/l and 2.0 U/l, respectively, and in aspartate transaminase (AST) of 2.7 U/l and 2.0 U/l, respectively, from baseline to end of study were seen in the canakinumab-treated groups versus the triamcinolone acetonide-treated group(s), however the incidence of clinically significant changes (≥ 3 x the upper limit of normal) was greater for patients treated with triamcinolone acetonide (2.5% for both AST and ALT) compared with canakinumab-treated patients (1.6% for ALT and 0.8% for AST).

Triglycerides

In active-controlled gouty arthritis trials, there was a mean increase in triglycerides of 33.5 mg/dl in canakinumab-treated patients compared with a modest decrease of -3.1 mg/dl with triamcinolone acetonide. The incidence of patients with triglyceride elevations > 5 x upper limit of normal (ULN) was 2.4% with canakinumab and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Long term data from observational study

A total of 243 CAPS patients (85 paediatric patients aged ≥ 2 to ≤ 17 years and 158 adult patients aged ≥ 18 years) were treated with canakinumab in routine clinical practice in a long-term registry study (mean of 3.8 years of canakinumab exposure). The safety profile of canakinumab observed following long-term treatment in this setting was consistent with what has been observed in interventional studies in CAPS patients.

Paediatric population

There were 80 paediatric CAPS patients (2-17 years of age) who received canakinumab in the interventional studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211), including the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract were the most frequently reported infection events.

Additionally, 6 paediatric patients under the age of 2 years were evaluated in a small open-label clinical study. The safety profile of canakinumab appeared similar to that in patients aged 2 years and above.

There were 102 TRAPS, HIDS/MKD and FMF patients (2-17 years of age) who received canakinumab in a 16-week study. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall population.

Elderly population

There is no significant difference in safety profile observed in patients ≥ 65 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC08

Mechanism of action

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

Pharmacodynamic effects

CAPS, TRAPS, HIDS/MKD and FMF

In clinical studies, CAPS, TRAPS, HIDS/MKD and FMF patients who have uncontrolled over-production of IL-1 beta show a rapid and sustained response to therapy with canakinumab, i.e. laboratory parameters such as high C-reactive protein (CRP) and serum amyloid A (SAA), high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

Still's disease (SJIA and AOSD)

Adult-onset Still's disease and systemic juvenile idiopathic arthritis are severe autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1-beta.

Common features of SJIA and AOSD 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 Clinical efficacy and safety).

Gouty arthritis

A gouty arthritis attack is caused by urate (monosodium urate monohydrate) crystals in the joint and surrounding tissue, which trigger resident macrophages to produce IL-1 beta via the "NALP3 inflammasome" complex. Activation of macrophages and concomitant over-production of IL-1 beta results in an acute painful inflammatory response. Other activators of the innate immune system, such as endogenous agonists of toll-like receptors, may contribute to the transcriptional activation of the IL-1 beta gene, initiating a gouty arthritis attack. Following canakinumab treatment, the inflammatory markers CRP or SAA and signs of acute inflammation (e.g. pain, swelling, redness) in the affected joint subside rapidly.

Clinical efficacy and safety

CAPS

The efficacy and safety of canakinumab have been demonstrated in a total of 211 adult and paediatric 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 canakinumab 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 normalised rapidly within days of canakinumab injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. an 8-week open-label period (Part I), a 24-week randomised, 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 canakinumab (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- Part I: A complete clinical and biomarker response to canakinumab (defined as composite of physician's global assessment on autoinflammatory and on skin disease \leq minimal and CRP or SAA values < 10 mg/litre) 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 the proportion of patients with a disease relapse/flare: none (0%) of the patients randomised to canakinumab flared, compared with 81% of the patients randomised 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 canakinumab extension.

Table 2 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 n(%)	Placebo N=16 n(%)	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 paediatric 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 8 weeks 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 \geq 15 kg and \leq 40 kg). An increased dose was administered more frequently to patients aged 2 to < 4 years and to patients with NOMID/CINCA symptoms compared with FCAS or MWS.

A 6-year observational registry study was conducted to provide data on the long-term safety and effectiveness of canakinumab treatment in paediatric and adult CAPS patients in routine clinical practice. The study included 243 CAPS patients (including 85 patients less than 18 years of age). Disease activity was rated as absent or mild/moderate in more than 90% of patients at all post-baseline time points in the study, and median serological markers of inflammation (CRP and SAA) were normal (< 10 mg/litre) at all post-baseline time points. Although approximately 22% of patients receiving canakinumab required dose adjustment, only a small percentage of patients (1.2%) discontinued canakinumab due to lack of therapeutic effect.

Paediatric population

The CAPS interventional trials with canakinumab included a total of 80 paediatric patients with an age range from 2 to 17 years (approximately half of them treated on an mg/kg basis). Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population. The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

A 56-week, open-label study was conducted to assess the efficacy, safety and tolerability of canakinumab in paediatric CAPS patients \leq 4 years of age. Seventeen patients (including 6 patients under the age of 2 years) were evaluated, using weight-based starting doses of 2-8 mg/kg. The study also evaluated the effect of canakinumab on the development of antibodies to standard childhood vaccines. No differences in safety or efficacy were observed in patients under the age of 2 years compared with patients aged 2 years and above. All patients who received non-live, standard of care childhood vaccinations (N=7) developed protective antibody levels.

TRAPS, HIDS/MKD and FMF

The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD and FMF were demonstrated in a single, pivotal, phase III, 4-part study (N2301) consisting of three separate disease cohorts.

- Part I: Patients in each disease cohort aged 2 years and older entered a 12-week screening period during which they were evaluated for the onset of disease flare.
- Part II: Patients at flare onset were randomised into a 16-week double-blind, placebo-controlled treatment period during which they received either 150 mg canakinumab (2 mg/kg for patients with body weight \leq 40 kg) subcutaneous (s.c.) or placebo every 4 weeks. Patients > 28 days but < 2 years of age were allowed to enter the study directly into an open-arm of Part II as non-randomised patients (and were excluded from the primary efficacy analysis).
- Part III: Patients who completed 16 weeks of treatment and were classified as responders were re-randomised into a 24-week, double-blind withdrawal period during which they received canakinumab 150 mg (2 mg/kg for patients \leq 40 kg) s.c. or placebo every 8 weeks.
- Part IV: All Part III patients treated with canakinumab were eligible to enter into a 72-week open-label treatment extension period.

A total of 185 patients aged 28 days and above were enrolled and a total of 181 patients aged 2 years and above were randomised in part II of the study.

The primary efficacy endpoint of the randomised treatment period (Part II) was the proportion of responders within each cohort who had resolution of their index disease flare at Day 15 and did not experience a new flare during the remainder of the 16-week treatment period (defined as complete response). Resolution of the index disease flare was defined as having a Physician's Global Assessment (PGA) of Disease Activity score < 2 ("minimal or no disease") and CRP within normal range (≤ 10 mg/l) or reduction $\geq 70\%$ from baseline. A new flare was defined as a PGA score ≥ 2 ("mild, moderate, or severe disease") and CRP ≥ 30 mg/l. Secondary endpoints, all based on week 16 results (end of Part II), included the proportion of patients who achieved a PGA score of < 2, the proportion of patients with serological remission (defined as CRP ≤ 10 mg/l), and the proportion of patients with a normalised SAA level (defined as SAA ≤ 10 mg/l).

For the primary efficacy endpoint, canakinumab was superior to placebo for all three disease cohorts. Canakinumab also demonstrated superior efficacy compared to placebo on the secondary endpoints of PGA < 2 and CRP ≤ 10 mg/l in all three cohorts. Higher proportions of patients had normalised SAA (≤ 10 mg/l) at week 16 with canakinumab treatment compared to placebo in all three cohorts, with a statistically significant difference observed in TRAPS patients (see Table 3 with study results below).

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

Phase III trial, pivotal, randomised placebo-controlled treatment period (Part II)			
	Canakinumab n/N (%)	Placebo n/N (%)	p-value
Primary endpoint (disease flare) - Proportion of patients who had index disease flare resolution at day 15 and did not experience a new flare during the remainder of the 16-week treatment period			
FMF	19/31 (61.29)	2/32 (6.25)	< 0.0001*
HIDS/MKD	13/37 (35.14)	2/35 (5.71)	0.0020*
TRAPS	10/22 (45.45)	2/24 (8.33)	0.0050*
Secondary endpoints (disease and inflammatory markers)			
Physician Global Assessment < 2			
FMF	20/31 (64.52)	3/32 (9.38)	< 0.0001**
HIDS/MKD	17/37 (45.95)	2/35 (5.71)	0.0006**
TRAPS	10/22 (45.45)	1/24 (4.17)	0.0028**
C-reactive protein ≤ 10 mg/l			
FMF	21/31 (67.74)	2/32 (6.25)	< 0.0001**
HIDS/MKD	15/37 (40.54)	2/35 (5.71)	0.0010**
TRAPS	8/22 (36.36)	2/24 (8.33)	0.0149**
Serum amyloid A ≤ 10 mg/l			
FMF	8/31 (25.81)	0/32 (0.00)	0.0286
HIDS/MKD	5/37 (13.51)	1/35 (2.86)	0.0778
TRAPS	6/22 (27.27)	0/24 (0.00)	0.0235**
n=number of responders; N=number of evaluable patients			
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test			
**Indicates statistical significance (one-sided) at the 0.025 level based on the logistic regression model with treatment group and baseline PGA, CRP or SAA respectively, as explanatory variables for each cohort			

Up-titration

In Part II of the study, patients treated with canakinumab who had persistent disease activity received an additional dose of 150 mg (or 2 mg/kg for patients ≤ 40 kg) within the first month. This additional dose could be provided as early as 7 days after the first treatment dose. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients ≤ 40 kg) every 4 weeks.

In an exploratory analysis of the primary endpoint, it was observed that in patients with an inadequate response after the first dose, an up-titration within the first month to a dose of 300 mg (or 4 mg/kg) every 4 weeks further improved flare control, reduced disease activity and normalised CRP and SAA levels.

Paediatric patients:

Two non-randomised HIDS/MKD patients aged > 28 days but < 2 years were included in the study and received canakinumab. One patient had resolution of index flare by day 15 after receiving one single dose of canakinumab 2 mg/kg, but discontinued treatment after this first dose due to serious adverse events (pancytopenia and hepatic failure). This patient presented at study entry with a history of immune thrombocytopenic purpura and an active medical condition of abnormal hepatic function. The second patient received a starting dose of canakinumab 2 mg/kg and an add-on dose of 2 mg/kg at week 3, and was up-titrated at week 5 to receive a dose of 4 mg/kg administered every 4 weeks until the end of Part II of the study. Resolution of disease flare was achieved by week 5 and the patient had not experienced any new flare at the end of Part II of the study (week 16).

Still's disease (SJIA and AOSD)

SJIA

The efficacy of canakinumab 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 of 8.5 years and mean disease duration of 3.5 years at baseline) and had active disease defined as ≥ 2 joints with active arthritis, fever and elevated CRP.

Study G2305

Study G2305 was a randomised, double-blind, placebo-controlled, 4-week study assessing the short-term efficacy of canakinumab in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) canakinumab or placebo. The primary objective was the proportion of patients at day 15 who achieved a minimum 30% improvement in the paediatric American College of Rheumatology (ACR) response criterion adapted to include absence of fever. Canakinumab treatment improved all paediatric ACR response scores as compared to placebo at days 15 and 29 (Table 4).

Table 4 Paediatric ACR response and disease status at days 15 and 29

	Day 15		Day 29	
	Canakinumab N=43	Placebo N=41	Canakinumab 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 significant ($p \leq 0.0001$)				

Results for the components of the adapted paediatric ACR which included systemic and arthritic components, were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were -67% and -73% for canakinumab (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for canakinumab (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among canakinumab treated patients was consistent at day 29.

Study G2301

Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by canakinumab. The study consisted of two parts with two independent primary endpoints (successful steroid taper and time to flare). In Part I (open label) 177 patients were enrolled and received 4 mg/kg (up to 300 mg) canakinumab administered every 4 weeks for up to 32 weeks. Patients in Part II (double-blind) received either canakinumab 4 mg/kg or placebo every 4 weeks until 37 flare events occurred.

Corticosteroid dose tapering:

Of the total 128 patients who entered Part I taking corticosteroids, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to flare:

Patients taking canakinumab in Part II had a 64% reduced risk of a flare event as compared to the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). Sixty-three of the 100 patients entering Part II, whether assigned to placebo or canakinumab, did not experience a flare over the observation period (up to a maximum of 80 weeks).

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

Treatment with canakinumab resulted in clinically relevant improvements in patients' physical function and quality of life. In study G2305, the Childhood Health Assessment Questionnaire Least Squares means improvement was 0.69 for canakinumab vs placebo representing 3.6 times the minimal clinically important difference of 0.19 (p=0.0002). The median improvement from baseline to end of Part I of study G2301 was 0.88 (79%). Statistically significant improvements in the Child Health Questionnaire-PF50 scores were reported for canakinumab vs placebo in study G2305 (physical p=0.0012; psychosocial well-being p=0.0017).

Pooled efficacy analysis

Data from the first 12 weeks of canakinumab treatment from studies G2305, G2301 and the extension study were pooled to assess maintenance of efficacy. These data showed similar improvements from baseline to week 12 in the adapted paediatric ACR responses and its components to those observed in the placebo controlled study (G2305). At week 12, the adapted paediatric ACR30, 50, 70, 90 and 100 responses were: 70%, 69%, 61%, 49% and 30%, respectively and 28% of patients had inactive disease (N=178).

Although limited, evidence from the clinical trials suggests that patients not responding to tocilizumab or anakinra may respond to canakinumab.

Study G2301E1

The efficacy observed in the studies G2305 and G2301 was maintained in the open-label long-term extension study G2301E1. Of the 270 SJIA patients in the study, 147 patients had received treatment with canakinumab in studies G2305 or G2301 (Cohort I), and 123 patients were canakinumab-naïve patients (Cohort II). Patients in Cohort I were treated for a median duration of 3.2 years (up to 5.2 years), and patients in Cohort II were treated for a median duration of 1.8 years (up to 2.8 years). In the extension study, all patients received canakinumab 4 mg/kg (up to maximum 300 mg) every 4 weeks. In both cohorts, patients who were well-controlled responders (retrospectively defined as adapted paediatric ACR \geq 90) and who did not require a concomitant corticosteroid were permitted to reduce their canakinumab dose to 2 mg/kg every 4 weeks (62/270; 23%).

Study G2306

Study G2306 was an open-label study to assess maintenance of treatment response with canakinumab dose reduction (2 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 8 weeks) in SJIA patients who were receiving canakinumab 4 mg/kg every 4 weeks. Seventy five patients aged 2 to 22 years who maintained inactive disease status for at least 6 consecutive months (clinical remission) with canakinumab monotherapy, including patients who were able to maintain inactive disease status with discontinuation of concomitant corticosteroid and/or methotrexate use for at least 4 weeks, were randomised to receive canakinumab 2 mg/kg every 4 weeks (N=38) or canakinumab 4 mg/kg every 8 weeks (N=37). After 24 weeks, 71% (27/38) of patients who received the reduced dose (2 mg/kg every 4 weeks) and 84% (31/37) of patients who received the prolonged dosing interval (4 mg/kg every 8 weeks) were able to maintain inactive disease status for 6 months. Of the patients in clinical remission who continued with further dose reduction (1 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 12 weeks), 93% (26/28) and 91% (30/33) of patients, respectively, were able to maintain inactive disease status for 6 months. Patients who maintained inactive disease status for 6 additional months at this lowest dose regimen were allowed to discontinue canakinumab. Overall, 33% (25/75) of patients randomised to dose reduction or dose interval prolongation arms were able to discontinue treatment with canakinumab and maintain inactive disease status for 6 months. The rate of adverse events in both treatment arms was similar to the rate seen in patients treated with canakinumab 4 mg/kg every 4 weeks.

AOSD

The efficacy of canakinumab 4 mg/kg (up to maximum 300 mg) administered every 4 weeks in AOSD patients in a randomised, double-blind placebo-controlled study in 36 patients (22 to 70 years old) was comparable to that observed in SJIA patients. In study GDE01T, a higher proportion of patients (12/18, 66.7%) in the canakinumab group than in the placebo group (7/17, 41.2%) demonstrated an improvement from baseline in Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28-ESR) of > 1.2 at week 12, which failed to reach statistical significance (odds ratio 2.86, treatment difference [%] 25.49 [95% CI: 9.43, 55.80]). By week 4, 7 of 18 patients (38.9%) treated with canakinumab had already achieved DAS28-ESR remission versus 2 of 17 patients (11.8%) on placebo. These data are consistent with the results of a pooled efficacy analysis of 418 SJIA patients which showed that the efficacy of canakinumab in a subset of SJIA patients aged 16 to < 20 years (n=34) was consistent with the efficacy observed in patients less than 16 years of age (n=384).

Gouty arthritis

The efficacy of canakinumab for the treatment of acute gouty arthritis attacks was demonstrated in two multicentre, randomised, double-blind, active-controlled studies in patients with frequent gouty arthritis (≥ 3 attacks in the previous 12 months) unable to use NSAIDs or colchicine (due to contraindication, intolerance or lack of efficacy). The studies were 12 weeks followed by 12-week double-blind extension. A total of 225 patients were treated with subcutaneous canakinumab 150 mg and 229 patients were treated with intramuscular triamcinolone acetonide (TA) 40 mg at study entry, and when experiencing a new attack thereafter. The mean number of gouty arthritis attacks in the previous 12 months was 6.5. Over 85% of patients had comorbidity, including hypertension (60%), diabetes (15%), ischaemic heart disease (12%), and stage ≥ 3 chronic kidney disease (25%). Approximately one-third of the patients enrolled (76 [33.8%] in the canakinumab group and 84 [36.7%] in the triamcinolone acetonide group) had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. Concomitant treatment with ULTs was reported by 42% of patients at entry.

The co-primary endpoints were: (i) gouty arthritis pain intensity (visual analogue scale, VAS) at 72 hours post-dose, and (ii) time to first new gouty arthritis attack.

For the overall study population, pain intensity was statistically significantly lower for canakinumab 150 mg compared with triamcinolone acetonide at 72 hours. Canakinumab also reduced the risk of subsequent attacks (see Table 5).

Efficacy results in a subgroup of patients unable to use both NSAIDs and colchicine and who were on ULT, failed ULT or had a contraindication to ULT (N=101) were consistent with the overall study population with a statistically significant difference compared to triamcinolone acetonide in pain intensity at 72 hours (-10.2 mm, p=0.0208) and in reduction of risk of subsequent attacks (Hazard ratio 0.39, p=0.0047 at 24 weeks).

Efficacy results for a more stringent subgroup limited to current users of ULT (N=62) are presented in Table 5. Treatment with canakinumab induced a reduction of pain and reduced the risk of subsequent attacks in patients using ULT and unable to use both NSAIDs and colchicine, although the observed treatment difference compared to triamcinolone acetonide was less pronounced than with the overall study population.

Table 5 Efficacy for the overall study population and in a subgroup of patients currently using ULT and unable to use both NSAIDs and colchicine

Efficacy endpoint	Overall study population; N=454	Unable to use both NSAIDs and colchicine; on ULT N=62
Treatment of gouty arthritis attacks as measured by pain intensity (VAS) at 72 h		
Least Squares mean estimated difference to triamcinolone acetonide	-10.7	-3.8
CI	(-15.4, -6.0)	(-16.7, 9.1)
p-value, 1-sided	p < 0.0001*	p=0.2798
Risk reduction of subsequent gouty arthritis attacks as measured by time to first new flare (24 weeks)		
Hazard ratio to triamcinolone acetonide	0.44	0.71
CI	(0.32, 0.60)	(0.29, 1.77)
p-value, 1-sided	p < 0.0001*	p=0.2337

* Denotes significant p-value ≤ 0.025

Safety results showed an increased incidence of adverse events for canakinumab compared to triamcinolone acetonide, with 66% vs 53% of patients reporting any adverse event and 20% vs 10% of patients reporting an infection adverse event over 24 weeks.

Elderly population

Overall, the efficacy, safety and tolerability profile of canakinumab in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)

In clinical studies, canakinumab has been safely administered with ULT. In the overall study population, patients on ULT had a less pronounced treatment difference in both pain reduction and reduction in the risk of subsequent gouty arthritis attacks compared to patients not on ULT.

Immunogenicity

Antibodies against canakinumab were observed in approximately 1.5%, 3% and 2% of the patients treated with canakinumab for CAPS, SJIA and gouty arthritis, respectively. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

There were no antibodies against canakinumab observed in TRAPS, HIDS/MKD and FMF patients treated with doses of 150 mg and 300 mg over 16 weeks of treatment.

Paediatric population

The Marketing Authorisation Holder has completed four Paediatric Investigation Plans for canakinumab (for CAPS, SJIA, FMF – HIDS/MKD and TRAPS respectively). This product information has been updated to include the results of studies with canakinumab in the paediatric population.

The European Medicines Agency has waived the obligation to submit the results of studies with canakinumab in all subsets of the paediatric population in gouty arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

CAPS

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. Mean values for C_{max} and AUC_{inf} after a single subcutaneous dose of 150 mg in a typical adult CAPS patient (70 kg) were 15.9 $\mu\text{g/ml}$ and 708 $\mu\text{g}\cdot\text{d/ml}$. The absolute bioavailability of subcutaneously administered 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. Predicted steady-state exposure values ($C_{min,ss}$, $C_{max,ss}$, $AUC_{ss,8w}$) after 150 mg subcutaneous administration (or 2 mg/kg, respectively) every 8 weeks were slightly higher in the weight category 40-70 kg (6.6 $\mu\text{g/ml}$, 24.3 $\mu\text{g/ml}$, 767 $\mu\text{g}\cdot\text{d/ml}$) compared to the weight categories < 40 kg (4.0 $\mu\text{g/ml}$, 19.9 $\mu\text{g/ml}$, 566 $\mu\text{g}\cdot\text{d/ml}$) and > 70 kg (4.6 $\mu\text{g/ml}$, 17.8 $\mu\text{g/ml}$, 545 $\mu\text{g}\cdot\text{d/ml}$). The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks.

Distribution

Canakinumab binds to serum IL-1 beta. The distribution volume (V_{ss}) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg.

Elimination

The apparent clearance (CL/F) of canakinumab increases with body weight. It was estimated to be 0.17 l/d in a CAPS patient of body weight 70 kg and 0.11 l/d in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS and SJIA 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.

TRAPS, HIDS/MKD and FMF

Bioavailability in TRAPS, HIDS/MKD and FMF patients has not been determined independently. Apparent clearance (CL/F) in the TRAPS, HIDS/MKD and FMF population at body weight of 55 kg (0.14 l/d) was comparable to CAPS population at body weight of 70 kg (0.17 l/d). The apparent volume of distribution (V/F) was 4.96 l at body weight of 55 kg.

After repeated subcutaneous administration of 150 mg every 4 weeks, canakinumab minimal concentration at week 16 (C_{min}) was estimated to be $15.4 \pm 6.6 \mu\text{g/ml}$. The estimated steady state AUC_{tau} was $636.7 \pm 260.2 \mu\text{g}\cdot\text{d/ml}$.

Still's disease (SJIA and AOSD)

Bioavailability in SJIA patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the SJIA and CAPS population (0.004 l/d per kg). The apparent volume of distribution per kg (V/F per kg) was 0.14 l/kg. Sparse pharmacokinetics (PK) data in AOSD patients suggest similar PK of canakinumab as compared to SJIA and other patient populations.

After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. The overall predicted mean (\pm SD) for $C_{\min,ss}$, $C_{\max,ss}$ and AUC_{ss4w} were 14.7 ± 8.8 μ g/ml, 36.5 ± 14.9 μ g/ml and 696.1 ± 326.5 μ g*d/ml, respectively.

The AUC_{ss4w} in each age group was 692, 615, 707 and 742 μ g*d/ml for 2-3, 4-5, 6-11, and 12-19 years old, respectively. When stratified by weight, a lower (30-40%) median of exposure for $C_{\min,ss}$ (11.4 vs 19 μ g/ml) and AUC_{ss} (594 vs 880 μ g*d/ml) for the lower bodyweight category (≤ 40 kg) vs the higher bodyweight category (> 40 kg) was observed.

Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Gouty arthritis population

Bioavailability in gouty arthritis patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the gouty arthritis and CAPS population (0.004 l/d/kg). Mean exposure in a typical gouty arthritis patient (93 kg) after a single subcutaneous 150 mg dose (C_{\max} : 10.8 μ g/ml and AUC_{inf} : 495 μ g*d/ml) was lower than in a typical 70 kg CAPS patient (15.9 μ g/ml and 708 μ g*d/ml). This is consistent with the observed increase in CL/F with body weight.

The expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.

Paediatric population

Peak concentrations of canakinumab occurred between 2 to 7 days (T_{\max}) following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in paediatric 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 pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in children aged 2 to < 4 years were similar to those in patients 4 years of age and older. Subcutaneous absorption rate was estimated to decrease with age and appeared to be fastest in the youngest patients. Accordingly, T_{\max} was shorter (3.6 days) in younger SJIA patients (2-3 years) compared to older SJIA patients (12-19 years; T_{\max} 6 days). Bioavailability (AUC_{ss}) was not affected.

An additional pharmacokinetics analysis showed that the pharmacokinetics of canakinumab in 6 paediatric CAPS patients under the age of 2 years were similar to the pharmacokinetics in paediatric patients 2-4 years of age. Based on the population pharmacokinetic modelling analysis, the expected exposures after a dose of 2 mg/kg were comparable across the CAPS paediatric age groups, but were approximately 40% lower in paediatric patients of very low body weight (e.g. 10 kg) than in adult patients (150 mg dose). This is consistent with the observations of higher exposure in higher body weight groups in CAPS patients.

In TRAPS, HIDS/MKD and FMF, exposure parameters (trough concentrations) were comparable across age groups from 2 to < 20 years old following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

Pharmacokinetic properties are similar in CAPS, TRAPS, HIDS/MKD, FMF and SJIA paediatric populations.

Elderly population

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of cross-reactivity, repeated dose toxicity, immunotoxicity, toxicity to reproduction and development.

Formal carcinogenicity studies have not been conducted with canakinumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

From a microbiological point of view, the product should be used immediately after first opening.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Solution for injection in a vial (type I glass) with a stopper (laminated chlorobutyl rubber) and flip-off cap (aluminium).

Packs containing 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ilaris 150 mg/ml solution for injection is supplied in a single-use vial for individual use.

Instructions for administration

Allow the vial to warm to room temperature before injection. The solution should be practically free of visible particles and clear to opalescent. The solution should be colourless or may have a slight brownish-yellow tint. Using an 18 G or 21 G x 2 inch needle (or similar as available on the market) and a 1 ml syringe, carefully withdraw the required volume depending on the dose to be administered. Once the required volume is withdrawn, recap and remove the withdrawal needle from the syringe and attach a 27 G x 0.5 inch needle (or similar as available on the market) to immediately inject the solution subcutaneously.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009

Date of latest renewal: 06 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharma S.A.S.
Centre de Biotechnologie
8, rue de l'Industrie
68330 Huningue
France

Name and address of the manufacturer responsible for batch release

Powder for solution for injection

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Solution for injection

Novartis Farmacéutica, S.A.
Gran Vía de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Lek Pharmaceuticals d.d.
Verovskova Ulica 57
1526 Ljubljana
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Ilaris are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Patient Reminder Card

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNIT PACK CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted solution should ideally be used immediately, but can still be used for up to 24 hours if stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ilaris 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

Multipack: 4 (4x1) vials.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted solution should ideally be used immediately, but can still be used for up to 24 hours if stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ilaris 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted solution should ideally be used immediately, but can still be used for up to 24 hours if stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ilaris 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilaris 150 mg powder for solution for injection
canakinumab
SC after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNIT PACK CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg/ml solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab in 1 ml of solution.

3. LIST OF EXCIPIENTS

Also contains: mannitol, histidine, histidine hydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
Single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after first opening.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilaris 150 mg/ml injection
canakinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ilaris 150 mg powder for solution for injection canakinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ilaris is and what it is used for
2. What you need to know before you use Ilaris
3. How to use Ilaris
4. Possible side effects
5. How to store Ilaris
6. Contents of the pack and other information

1. What Ilaris is and what it is used for

What Ilaris is

Ilaris contains the active substance canakinumab, a monoclonal antibody that belongs to a group of medicines called interleukin inhibitors. It blocks the activity of a substance called interleukin-1 beta (IL-1 beta) in the body, which is present at increased levels in inflammatory diseases.

What Ilaris is used for

Ilaris is used for treatment of the following inflammatory diseases:

- Periodic fever syndromes:
 - Cryopyrin-associated periodic syndromes (CAPS),
 - Tumour necrosis factor receptor associated periodic syndrome (TRAPS),
 - Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD),
 - Familial Mediterranean fever (FMF).
- Still's disease including adult onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA)
- Gouty arthritis

More information on each of these diseases is given below.

Periodic fever syndromes

Ilaris is used in adults and children aged 2 years and older to treat the following:

- Cryopyrin-associated periodic syndromes (CAPS) – this is a group of auto-inflammatory diseases, which include:
 - Muckle-Wells syndrome (MWS),
 - Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological, cutaneous, articular syndrome (CINCA),
 - Severe forms of familial cold auto-inflammatory 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) also known as mevalonate kinase deficiency (MKD)
- Familial Mediterranean fever (FMF): Ilaris is used to treat FMF. Ilaris can be used together with colchicine, if appropriate.

In patients with periodic fever syndromes (CAPS, TRAPS, HIDS/MKD and FMF), the body produces too much IL-1 beta. This may cause fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Ilaris may improve these symptoms.

Still's disease

Ilaris is used in adults, adolescents and children to treat active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older if other treatments have not worked well enough. Ilaris can be used alone or in combination with methotrexate.

Still's disease including SJIA and AOSD is an inflammatory disease that can cause pain, swelling and inflammation of one or more joints, as well as rash and fever. A pro-inflammatory protein called IL-1 beta plays an important role in Still's disease inflammation. Ilaris blocks the activity of IL-1 beta, which may improve the signs and symptoms of Still's disease.

Gouty arthritis

Ilaris is used in adults to treat the symptoms of frequent gouty arthritis attacks if other treatments have not worked well enough.

Gouty arthritis is caused by the formation of urate crystals. These crystals cause excessive production of IL-1 beta, which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint (known as a gouty arthritis attack). By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

2. What you need to know before you use Ilaris

Do not use Ilaris

- if you are allergic to canakinumab or any of the other ingredients of this medicine (listed in section 6).
- if you have, or suspect you have, an active and severe infection.

Warning and precautions

Talk to your doctor before using Ilaris if any of the following applies to you:

- if you currently have an infection or if you have had repeated infections or a condition such as a known low level of white blood cells which makes you more likely to get infections.
- if you have or have ever had tuberculosis or direct contact with a person with an active tuberculosis infection. Your doctor may check whether you have tuberculosis using a specific test.
- if you have signs of a liver disorder such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
- if you need to have any vaccinations. You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris (see also “Other medicines and Ilaris”).

Contact your doctor immediately

- If you have ever developed an atypical, widespread rash or skin peeling after taking Ilaris. The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Ilaris treatment, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

Still’s disease

- Patients with Still’s disease may develop a condition called macrophage activation syndrome (MAS), which can be life-threatening. Your doctor will monitor you for potential triggering factors of MAS that include infections and re-activation of the underlying Still’s disease (flare).

Children and adolescents

- **CAPS, TRAPS, HIDS/MKD, FMF and SJIA:** Ilaris can be used in children aged 2 years and older.
- **Gouty arthritis:** Ilaris is not recommended for children or adolescents under 18 years of age.

Other medicines and Ilaris

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

- **Live vaccines:** You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while you are being treated with Ilaris. Your doctor may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris. If you need to be given a live vaccine after starting treatment with Ilaris, discuss this with your doctor. A live vaccine should normally be given 3 months after your last injection of Ilaris and 3 months before the next one.
- **Medicines called tumour necrosis factor (TNF) inhibitors,** such as etanercept, adalimumab or infliximab. These are used mainly in rheumatic and autoimmune diseases. They should not be used with Ilaris because this may increase the risk of infections.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- You are advised to avoid becoming pregnant and must use adequate contraception while using Ilaris and for at least 3 months after the last Ilaris treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risks of taking Ilaris during pregnancy.
- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of canakinumab before giving birth.
- It is not known whether Ilaris passes into human milk. Your doctor will discuss with you the potential risks of taking Ilaris before breast-feeding.

Driving and using machines

Ilaris treatment may give you a spinning sensation (dizziness or vertigo) or intense tiredness (asthenia). This may affect your ability to drive or use tools or machines. If you feel a spinning sensation or feel tired, do not drive or use any tools or machines until you are feeling normal again.

3. How to use Ilaris

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Keep your doctor informed of your condition and any symptoms before you use or are given Ilaris (see section 2). Your doctor may decide to delay or interrupt your treatment, but only if necessary.

Ilaris is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

If you have gouty arthritis, your treatment will be overseen by a doctor with specialist training. Ilaris should be injected by a healthcare professional only.

If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), you may inject yourself with Ilaris after proper training, or a caregiver may inject it for you.

How much Ilaris to use

Cryopyrin-associated periodic syndromes (CAPS)

The recommended starting dose of Ilaris is:

- *Adults and children aged 4 years or more*
 - 150 mg for patients who weigh more than 40 kg
 - 2 mg/kg for patients who weigh between 15 kg and 40 kg
 - 4 mg/kg for patients who weigh between 7.5 kg and less than 15 kg
- *Children aged 2 or 3 years*
 - 4 mg/kg for patients with body weight of 7.5 kg or more

Ilaris is injected every 8 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to the second dose, your treatment will be continued with 300 mg or 4 mg/kg every 8 weeks.
- If you do not respond well enough to the second dose, a third dose of Ilaris at 300 mg or 4 mg/kg may be given.
- If you respond well enough to the third dose, your treatment will be continued at 600 mg or 8 mg/kg every 8 weeks.

For children given a starting dose of 4 mg/kg who have not responded well enough after 7 days, the doctor may give a second dose of 4 mg/kg. If the child responds well enough to this, treatment may be continued with a dose of 8 mg/kg every 8 weeks.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) and familial Mediterranean fever (FMF)

The recommended starting dose of Ilaris is:

- *Adults and children aged 2 years or more*
 - 150 mg for patients who weigh more than 40 kg
 - 2 mg/kg for patients who weigh between 7.5 kg and less than 40 kg

Ilaris is injected every 4 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to this, your treatment will be continued with 300 mg or 4 mg/kg every 4 weeks.

Still's disease (SJIA and AOSD)

The recommended dose of Ilaris for patients with Still's disease with body weight of 7.5 kg and above is 4 mg/kg (up to a maximum of 300 mg). Ilaris is injected every 4 weeks as a single dose.

Gouty arthritis

Your doctor will discuss with you the need to start or adjust a urate lowering therapy to lower the uric acid level in your blood.

The recommended dose of Ilaris for adult gouty arthritis patients is 150 mg given as a single dose at the time of a gouty arthritis attack.

If you need another treatment with Ilaris, and got relief from the last dose, you must wait at least 12 weeks before the next dose.

Injecting Ilaris yourself or injecting a patient with Ilaris

If you are a patient with CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), or a caregiver of a patient with one of these conditions, you may administer Ilaris injections yourself after proper training in the correct injection technique.

- The patient or caregiver and the doctor should decide together who will administer the Ilaris injections.
- The doctor or nurse will demonstrate how to administer Ilaris injections.
- Do not try to administer an injection 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 is supplied in a single-use vial for individual use.
- Never re-use the leftover solution.

For instructions on how to administer Ilaris injections, please read the section "Instructions for use" at the end of this leaflet. If you have any questions, talk to your doctor, pharmacist or nurse.

How long to use Ilaris

- **CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA):** You should continue using Ilaris for as long as the doctor tells you.
- **Gouty arthritis:** If you have a gouty arthritis attack, you will be given a single dose of Ilaris. If you experience a new attack, your doctor may consider giving you a new dose of Ilaris but not earlier than 12 weeks from the previous dose.

If you use more Ilaris than you should

If you accidentally inject more Ilaris than the recommended dose, it is unlikely to be serious, but you should inform your doctor, pharmacist or nurse as soon as possible.

If you forget to use Ilaris

If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA) and have forgotten to inject a dose of Ilaris, inject the next dose as soon as you remember. Then talk to the doctor to discuss when you should inject the next dose. You should then continue with injections at the recommended intervals as before.

If you stop using Ilaris

Stopping your treatment with Ilaris may cause your condition to get worse. Do not stop taking Ilaris unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. Tell your doctor immediately, if you notice any of the side effects below:

- Fever lasting longer than 3 days or any other symptoms that might suggest a serious infection. These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, sore throat or mouth ulcers, cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin or inflammation of connective tissue (cellulitis). These symptoms could be due to a serious infection, an unusual infection (opportunistic infection) or be related to low levels of white blood cells (called leukopenia or neutropenia). Your doctor may check your blood regularly if considered necessary.
- Allergic reactions with rash and itching and possibly also hives, difficulty breathing or swallowing, dizziness, unusual awareness of your heart beat (palpitations) or low blood pressure.

Other side effects of Ilaris include:**Very common** (may affect more than 1 in 10 people):

- Infections of any kind. These can include:
 - Respiratory infections such as chest infection, flu, sore throat, runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks or forehead with or without fever (pneumonia, bronchitis, influenza, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infection).
 - Other infections such as ear infection, skin infection (cellulitis), stomach pain and feeling sick (gastroenteritis) and painful and frequent urination with or without fever (urinary tract infection).
- Upper abdominal pain.
- Pain in joints (arthralgia).
- Drop in level of white blood cells (leukopenia).
- Abnormal kidney function test results (creatinine renal clearance decreased, proteinuria).
- Injection site reaction (such as redness, swelling, warmth and itching).

Common (may affect up to 1 in 10 people):

- Candida - vaginal yeast infection (vulvovaginal candidiasis).
- Feeling dizzy, spinning sensation (dizziness or vertigo).
- Pain in the back or muscles.
- Feeling weak or very tired (fatigue, asthenia).
- Drop in level of white blood cells which help prevent infection (neutropenia).
- Abnormal levels of triglycerides in your blood (lipid metabolism disorder).
- Abnormal liver function test results (transaminases increased) or high level of bilirubin in the blood, with or without yellow skin and eyes (hyperbilirubinaemia).

Uncommon (may affect up to 1 in 100 people):

- Heartburn (gastro-oesophageal reflux disease).
- Drop in level of blood cells which help prevent bleeding (platelets).

Tell your doctor or your child's doctor immediately if you notice any of these symptoms.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ilaris

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Store in the original package in order to protect from light.
- After mixing (reconstitution) the medicine should be used immediately. If not used immediately, the solution should be stored in the refrigerator (2°C - 8°C) and used within 24 hours.
- Do not use this medicine if you notice that the solution is not clear to opalescent or contains particles.
- Any unused medicine must be discarded after the dose has been injected.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ilaris contains

- The active substance is canakinumab. One vial of powder contains 150 mg canakinumab. After reconstitution, each ml of solution contains 150 mg canakinumab.
- The other ingredients are: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

What Ilaris looks like and contents of the pack

- Ilaris is supplied as a powder for solution for injection (150 mg in a 6 ml glass vial).
- The powder is white.
- Ilaris is available in packs containing one vial or multipacks comprising four intermediate packs, each containing one vial. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tel: +370 5 269 16 50

Luxembourg/Luxemburg

Novartis Pharma N.V.
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>

Instructions for use of Ilaris powder for solution for injection

Please note that the preparation of the injection takes about 30 minutes.
See also section 3, “Injecting Ilaris yourself or injecting a patient with Ilaris”.

Read these instructions all the way through before beginning.

Essential preparation

- Find a clean place in which to prepare and administer the injection.
- Wash your hands with soap and water.
- Check the expiry dates on the vial and syringes. Do not use after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Always use new, unopened needles and syringes. Avoid touching the needles and the tops of the vials.

Gather together the necessary items

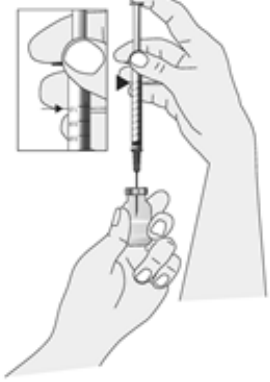
Included in the pack

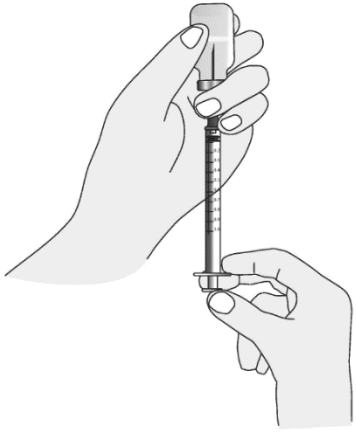
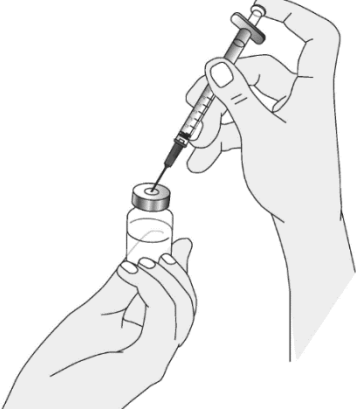

- one vial of Ilaris powder for solution for injection (keep refrigerated)

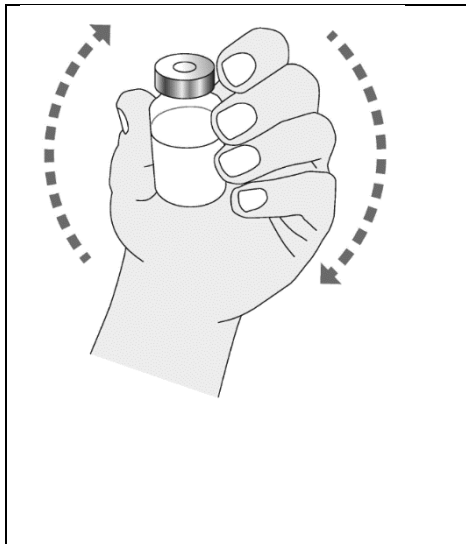
Not included in the pack

- one vial (or ampoule) of sterile water for injections (“water”) (at room temperature)
- one 1.0 ml syringe
- one 18 G x 2 inch (50 mm) needle for reconstituting the powder (“transfer needle”)
- one 27 G x 0.5 inch (13 mm) needle for injecting (“injection needle”)
- alcohol swabs
- clean, dry cotton swabs
- an adhesive plaster
- a proper disposal container for used needles, syringe and vials (sharps container)

Mixing Ilaris

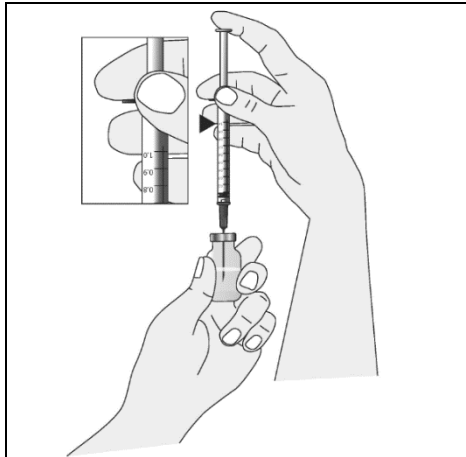
	<ol style="list-style-type: none">1. Remove the caps from the Ilaris and water vials. Do not touch the vial stoppers. Clean the stoppers with the alcohol swab.2. Open the wrappers containing the syringe and the transfer needle (the 50 mm needle) and attach the needle to the syringe.3. Carefully remove 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.4. Gently push the plunger all the way down until air is in the vial.
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	<ol style="list-style-type: none"> 5. Turn the vial and syringe upside down and bring to eye level. 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 professional or pharmacist. 7. Make sure 1.0 ml of water is in the syringe, then take the needle out of the vial. (There will be water remaining in the vial.)
	<ol style="list-style-type: none"> 8. Insert the transfer needle through the centre of the stopper of the vial of Ilaris powder, taking care not to touch the needle or the stopper. Slowly inject the water into the vial containing the Ilaris powder. 9. Carefully remove the transfer needle from the vial and recap the needle as instructed by your healthcare provider or pharmacist.
	<ol style="list-style-type: none"> 10. Without touching the rubber stopper, swirl (do not shake) the vial slowly at an angle of about 45 degrees for about 1 minute. Allow to stand for 5 minutes.

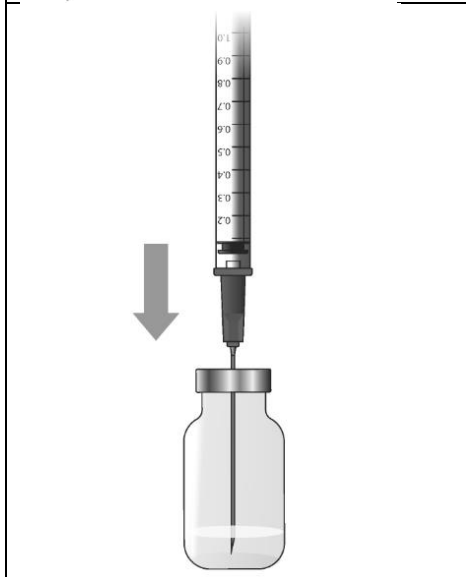


11. Now, gently turn the vial upside down and back again ten times, again taking care not to touch the rubber stopper.
12. Allow to stand for about 15 minutes at room temperature to get a clear to opalescent solution. Do not shake. Do not use if particles are present in the solution.
13. Make sure all 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 free of visible particles. The solution should be colourless or may have a slight brownish-yellow tint.
 - If not used immediately after mixing, the solution should be stored in the refrigerator (2°C to 8°C) and used within 24 hours.

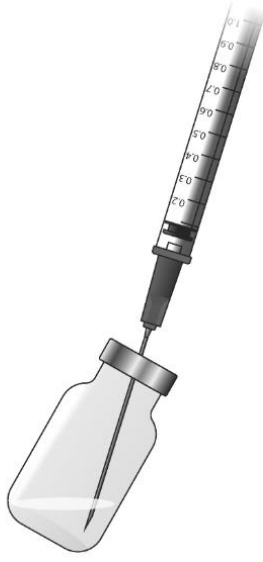
Preparing the injection





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. The needle should not be in the liquid at this point. Gently push the plunger all the way down until all of the air is injected into the vial. Do not inject air into the liquid.




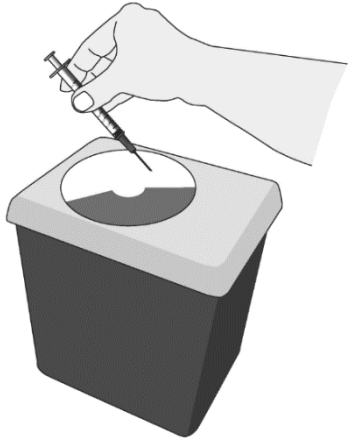
16. **Do not** turn the vial and syringe upside down, the vial should stay upright. Insert the needle all the way into the vial until it reaches the bottom edge.

	<ol style="list-style-type: none"> 17. Tip the vial to ensure that the required amount of solution can be drawn into the syringe 18. NOTE: The required amount depends on the dose to be administered. Your healthcare provider will instruct you on the right amount for you. 19. Slowly pull the syringe plunger up to the correct mark (amount to be given), 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. 20. 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. 21. Open the wrapper containing the injection needle and attach the needle to the syringe. Set the syringe aside.
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Giving the injection

	<ol style="list-style-type: none"> 22. Choose an injection site on the upper thigh, abdomen, upper arm or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Do not inject into scar-tissue as this may mean you do not get all of your medicine. Avoid injecting into a vein. 23. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle. 24. 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.
	<ol style="list-style-type: none"> 25. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty. 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

	<p>26. 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. Then apply an adhesive plaster.</p>
	<p>27. Safely dispose of needles and syringe in the sharps container or as directed by your healthcare provider or pharmacist. Never re-use syringes or needles.</p> <p>28. Properly dispose of vials containing remaining water and Ilaris solution (if any) as directed by your healthcare provider or pharmacist. Any unused product or waste material should be disposed of in accordance with local requirements.</p> <p>Keep the sharps container out of reach of children.</p> <p>Dispose of it as directed by your healthcare provider or pharmacist.</p>

Package leaflet: Information for the user

Ilaris 150 mg/ml solution for injection canakinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ilaris is and what it is used for
2. What you need to know before you use Ilaris
3. How to use Ilaris
4. Possible side effects
5. How to store Ilaris
6. Contents of the pack and other information

1. What Ilaris is and what it is used for

What Ilaris is

Ilaris contains the active substance canakinumab, a monoclonal antibody that belongs to a group of medicines called interleukin inhibitors. It blocks the activity of a substance called interleukin-1 beta (IL-1 beta) in the body, which is present at increased levels in inflammatory diseases.

What Ilaris is used for

Ilaris is used for treatment of the following inflammatory diseases:

- Periodic fever syndromes:
 - Cryopyrin-associated periodic syndromes (CAPS),
 - Tumour necrosis factor receptor associated periodic syndrome (TRAPS),
 - Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD),
 - Familial Mediterranean fever (FMF).
- Still's disease including adult onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA)
- Gouty arthritis

More information on each of these diseases is given below.

Periodic fever syndromes

Ilaris is used in adults and children aged 2 years and older to treat the following:

- Cryopyrin-associated periodic syndromes (CAPS) – this is a group of auto-inflammatory diseases, which include:
 - Muckle-Wells syndrome (MWS),
 - Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological, cutaneous, articular syndrome (CINCA),
 - Severe forms of familial cold auto-inflammatory 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) also known as mevalonate kinase deficiency (MKD)
- Familial Mediterranean fever (FMF): Ilaris is used to treat FMF. Ilaris can be used together with colchicine, if appropriate.

In patients with periodic fever syndromes (CAPS, TRAPS, HIDS/MKD and FMF), the body produces too much IL-1 beta. This may cause fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Ilaris may improve these symptoms.

Still's disease

Ilaris is used in adults, adolescents and children to treat active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older if other treatments have not worked well enough. Ilaris can be used alone or in combination with methotrexate.

Still's disease including SJIA and AOSD is an inflammatory disease that can cause pain, swelling and inflammation of one or more joints, as well as rash and fever. A pro-inflammatory protein called IL-1 beta plays an important role in Still's disease inflammation. Ilaris blocks the activity of IL-1 beta, which may improve the signs and symptoms of Still's disease.

Gouty arthritis

Ilaris is used in adults to treat the symptoms of frequent gouty arthritis attacks if other treatments have not worked well enough.

Gouty arthritis is caused by the formation of urate crystals. These crystals cause excessive production of IL-1 beta, which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint (known as a gouty arthritis attack). By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

2. What you need to know before you use Ilaris

Do not use Ilaris

- if you are allergic to canakinumab or any of the other ingredients of this medicine (listed in section 6).
- if you have, or suspect you have, an active and severe infection.

Warning and precautions

Talk to your doctor before using Ilaris if any of the following applies to you:

- if you currently have an infection or if you have had repeated infections or a condition such as a known low level of white blood cells which makes you more likely to get infections.
- if you have or have ever had tuberculosis or direct contact with a person with an active tuberculosis infection. Your doctor may check whether you have tuberculosis using a specific test.
- if you have signs of a liver disorder such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
- if you need to have any vaccinations. You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris (see also “Other medicines and Ilaris”).

Contact your doctor immediately

- If you have ever developed an atypical, widespread rash or skin peeling after taking Ilaris. The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Ilaris treatment, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

Still’s disease

- Patients with Still’s disease may develop a condition called macrophage activation syndrome (MAS), which can be life-threatening. Your doctor will monitor you for potential triggering factors of MAS that include infections and re-activation of the underlying Still’s disease (flare).

Children and adolescents

- **CAPS, TRAPS, HIDS/MKD, FMF and SJIA:** Ilaris can be used in children aged 2 years and older.
- **Gouty arthritis:** Ilaris is not recommended for children or adolescents under 18 years of age.

Other medicines and Ilaris

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

- Live vaccines: You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while you are being treated with Ilaris. Your doctor may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris. If you need to be given a live vaccine after starting treatment with Ilaris, discuss this with your doctor. A live vaccine should normally be given 3 months after your last injection of Ilaris and 3 months before the next one.
- Medicines called tumour necrosis factor (TNF) inhibitors, such as etanercept, adalimumab or infliximab. These are used mainly in rheumatic and autoimmune diseases. They should not be used with Ilaris because this may increase the risk of infections.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- You are advised to avoid becoming pregnant and must use adequate contraception while using Ilaris and for at least 3 months after the last Ilaris treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risks of taking Ilaris during pregnancy.
- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of canakinumab before giving birth.
- It is not known whether Ilaris passes into human milk. Your doctor will discuss with you the potential risks of taking Ilaris before breast-feeding.

Driving and using machines

Ilaris treatment may give you a spinning sensation (dizziness or vertigo) or intense tiredness (asthenia). This may affect your ability to drive or use tools or machines. If you feel a spinning sensation or feel tired, do not drive or use any tools or machines until you are feeling normal again.

3. How to use Ilaris

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Keep your doctor informed of your condition and any symptoms before you use or are given Ilaris (see section 2). Your doctor may decide to delay or interrupt your treatment, but only if necessary.

Ilaris is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

If you have gouty arthritis, your treatment will be overseen by a doctor with specialist training. Ilaris should be injected by a healthcare professional only.

If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), you may inject yourself with Ilaris after proper training, or a caregiver may inject it for you.

How much Ilaris to use

Cryopyrin- associated periodic syndromes (CAPS)

The recommended starting dose of Ilaris is:

- *Adults and children aged 4 years or more*
 - 150 mg for patients who weigh more than 40 kg
 - 2 mg/kg for patients who weigh between 15 kg and 40 kg
 - 4 mg/kg for patients who weigh between 7.5 kg and less than 15 kg
- *Children aged 2 or 3 years*
 - 4 mg/kg for patients with body weight of 7.5 kg or more

Ilaris is injected every 8 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to the second dose, your treatment will be continued with 300 mg or 4 mg/kg every 8 weeks.
- If you do not respond well enough to the second dose, a third dose of Ilaris at 300 mg or 4 mg/kg may be given.
- If you respond well enough to the third dose, your treatment will be continued at 600 mg or 8 mg/kg every 8 weeks.

For children given a starting dose of 4 mg/kg who have not responded well enough after 7 days, the doctor may give a second dose of 4 mg/kg. If the child responds well enough to this, treatment may be continued with a dose of 8 mg/kg every 8 weeks.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) and familial Mediterranean fever (FMF)

The recommended starting dose of Ilaris is:

- *Adults and children aged 2 years or more*
 - 150 mg for patients who weigh more than 40 kg
 - 2 mg/kg for patients who weigh between 7.5 kg and less than 40 kg

Ilaris is injected every 4 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to this, your treatment will be continued with 300 mg or 4 mg/kg every 4 weeks.

Still's disease (SJIA and AOSD)

The recommended dose of Ilaris for patients with Still's disease with body weight of 7.5 kg and above is 4 mg/kg (up to a maximum of 300 mg). Ilaris is injected every 4 weeks as a single dose.

Gouty arthritis

Your doctor will discuss with you the need to start or adjust a urate lowering therapy to lower the uric acid level in your blood.

The recommended dose of Ilaris for adult gouty arthritis patients is 150 mg given as a single dose at the time of a gouty arthritis attack.

If you need another treatment with Ilaris, and got relief from the last dose, you must wait at least 12 weeks before the next dose.

Injecting Ilaris yourself or injecting a patient with Ilaris

If you are a patient with CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), or a caregiver of a patient with one of these conditions, you may administer Ilaris injections yourself after proper training in the correct injection technique.

- The patient or caregiver and the doctor should decide together who will administer the Ilaris injections.
- The doctor or nurse will demonstrate how to administer Ilaris injections.
- Do not try to administer an injection yourself if you have not been properly trained or if you are not sure how to do it.
- Ilaris 150 mg/ml solution for injection is supplied in a single-use vial for individual use.
- Never re-use the leftover solution.

For instructions on how to administer Ilaris injections, please read the section “Instructions for use” at the end of this leaflet. If you have any questions, talk to your doctor, pharmacist or nurse.

How long to use Ilaris

- **CAPS, TRAPS, HIDS/MKD, FMF or Still’s disease (AOSD or SJIA):** You should continue using Ilaris for as long as the doctor tells you.
- **Gouty arthritis:** If you have a gouty arthritis attack, you will be given a single dose of Ilaris. If you experience a new attack, your doctor may consider giving you a new dose of Ilaris but not earlier than 12 weeks from the previous dose.

If you use more Ilaris than you should

If you accidentally inject more Ilaris than the recommended dose, it is unlikely to be serious, but you should inform your doctor, pharmacist or nurse as soon as possible.

If you forget to use Ilaris

If you have CAPS, TRAPS, HIDS/MKD, FMF or Still’s disease (AOSD or SJIA) and have forgotten to inject a dose of Ilaris, inject the next dose as soon as you remember. Then talk to the doctor to discuss when you should inject the next dose. You should then continue with injections at the recommended intervals as before.

If you stop using Ilaris

Stopping your treatment with Ilaris may cause your condition to get worse. Do not stop taking Ilaris unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. Tell your doctor immediately, if you notice any of the side effects below:

- Fever lasting longer than 3 days or any other symptoms that might suggest a serious infection. These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, sore throat or mouth ulcers, cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin or inflammation of connective tissue (cellulitis). These symptoms could be due to a serious infection, an unusual infection (opportunistic infection) or be related to low levels of white blood cells (called leukopenia or neutropenia). Your doctor may check your blood regularly if considered necessary.
- Allergic reactions with rash and itching and possibly also hives, difficulty breathing or swallowing, dizziness, unusual awareness of your heart beat (palpitations) or low blood pressure.

Other side effects of Ilaris include:

Very common (may affect more than 1 in 10 people):

- Infections of any kind. These can include:
 - Respiratory infections such as chest infection, flu, sore throat, runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks or forehead with or without fever (pneumonia, bronchitis, influenza, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infection).
 - Other infections such as ear infection, skin infection (cellulitis), stomach pain and feeling sick (gastroenteritis) and painful and frequent urination with or without fever (urinary tract infection).
- Upper abdominal pain.
- Pain in joints (arthralgia).
- Drop in level of white blood cells (leukopenia).
- Abnormal kidney function test results (creatinine renal clearance decreased, proteinuria).
- Injection site reaction (such as redness, swelling, warmth and itching).

Common (may affect up to 1 in 10 people):

- Candida - vaginal yeast infection (vulvovaginal candidiasis).
- Feeling dizzy, spinning sensation (dizziness or vertigo).
- Pain in the back or muscles.
- Feeling weak or very tired (fatigue, asthenia).
- Drop in level of white blood cells which help prevent infection (neutropenia).
- Abnormal levels of triglycerides in your blood (lipid metabolism disorder).
- Abnormal liver function test results (transaminases increased) or high level of bilirubin in the blood, with or without yellow skin and eyes (hyperbilirubinaemia).

Uncommon (may affect up to 1 in 100 people):

- Heartburn (gastro-oesophageal reflux disease).
- Drop in level of blood cells which help prevent bleeding (platelets).

Tell your doctor or your child's doctor immediately if you notice any of these symptoms.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ilaris

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- The solution should be used immediately after first piercing the vial stopper to prepare the injection.
- Do not use this medicine if you notice that the solution is not clear to opalescent or contains particles.
- Any unused medicine must be discarded after withdrawal of the dose.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ilaris contains

- The active substance is canakinumab. One vial contains 150 mg canakinumab in 1 ml of solution.
- The other ingredients are mannitol, histidine, histidine hydrochloride monohydrate, polysorbate 80, water for injections.

What Ilaris looks like and contents of the pack

- Ilaris is supplied as a solution for injection in a 2 ml glass vial.
- The solution is a clear to opalescent liquid. It is colourless to slightly brownish-yellow. Do not use if the liquid contains easily visible particles, is cloudy or is distinctly brown.
- Ilaris is available in packs containing one vial.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

Instructions for use of Ilaris solution for injection

Read all the way through these instructions before injecting.

- It is important not to try to inject yourself until you have been trained by your healthcare professional.
- See also section 3, “Injecting Ilaris yourself or injecting a patient with Ilaris”.

Essential preparation

- Find a clean place in which to prepare and give yourself the injection.
- Wash your hands with soap and water, then dry them on a clean towel.
- After removing the vial from the refrigerator, check the expiry date on the vial. Do not use after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Let the vial stand unopened for 10 minutes to bring the contents to room temperature. Do not try to heat the vial. Let it warm up on its own.
- Always use new, unopened needles and syringes. Do not touch the needles or the top of the vial.

Gather together the necessary items

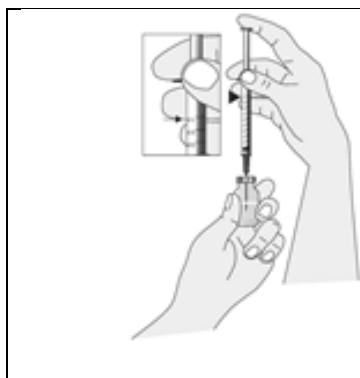
Included in the pack

- one vial of Ilaris solution for injection (keep refrigerated)

Not included in the pack

- one 1.0 ml syringe
- one needle (such as 18 G or 21 G x 2 inch or similar, as available on the market) to draw up the solution from the vial (“withdrawal needle”).
- one 27 G x 0.5 inch (or similar, as available on the market) needle for injecting (“injection needle”)
- alcohol swabs
- clean, dry cotton swabs
- an adhesive plaster
- a proper disposal container for used needles, syringe and vial (sharps container)

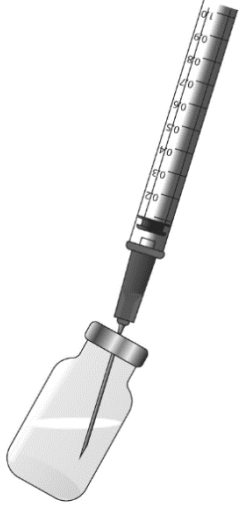
Preparing the injection





1. Take off the protective cap from the Ilaris vial. Do not touch the vial stopper. Clean the rubber stopper of the vial with an alcohol swab.

Open the wrappers containing the syringe and the withdrawal needle.



- Put the withdrawal needle on the syringe.
- Take off the cap from the withdrawal needle.
- Push the withdrawal needle into the vial of Ilaris solution through the centre of the rubber stopper.

	<ol style="list-style-type: none"> 2. Tip the vial to ensure that the required amount of solution can be drawn into the syringe. NOTE: The required amount depends on the dose to be administered. Your healthcare provider will instruct you on the right amount for you. 3. Slowly pull the syringe plunger up to the correct mark (amount to be given as per healthcare provider's instructions), 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. 4. Remove the syringe and withdrawal needle from the vial. (There may be solution remaining in the vial.) Recap the withdrawal needle as instructed by your healthcare provider or pharmacist. Remove the withdrawal needle from the syringe and place it in the sharps container. 5. Open the wrapper containing the injection needle and attach the needle to the syringe. Immediately proceed to administering the injection.
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Giving the injection

	<ol style="list-style-type: none"> 6. Choose an injection site on the upper thigh, abdomen, upper arm or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Do not inject into scar tissue as this may mean you do not get all of your medicine. Avoid injecting into a vein. 7. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle. 8. 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.
	<ol style="list-style-type: none"> 9. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty. 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

	<p>10. 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. Then apply an adhesive plaster.</p>
	<p>11. Safely dispose of needles and syringe in the sharps container or as directed by your healthcare provider or pharmacist. Never re-use syringes or needles.</p> <p>12. Properly dispose of vials containing remaining Ilaris solution (if any) as directed by your healthcare provider or pharmacist. Any unused product or waste material should be disposed of in accordance with local requirements. Never re-use the leftover solution.</p> <p>Keep the sharps container out of reach of children.</p> <p>Dispose of it as directed by your healthcare provider or pharmacist.</p>