The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in March 2017

1. NAME OF THE MEDICINAL PRODUCT

ILARIS®150 mg/mL

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.
Each vial contains 92.35 mg of sucrose.

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 (CAPS)
Ilaris is indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above, 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) in patients in whom colchicine

is contraindicated, is not tolerated, or does not provide an adequate response despite the highest tolerable dose of colchicine.
Ilaris can be given as monotherapy or in combination with colchicine.

Ilaris is also indicated for the treatment of:

Systemic Juvenile Idiopathic Arthritis (SJIA)

Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 4 years and older.

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 SJIA, 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.

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

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

The recommended starting dose of Ilaris 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:

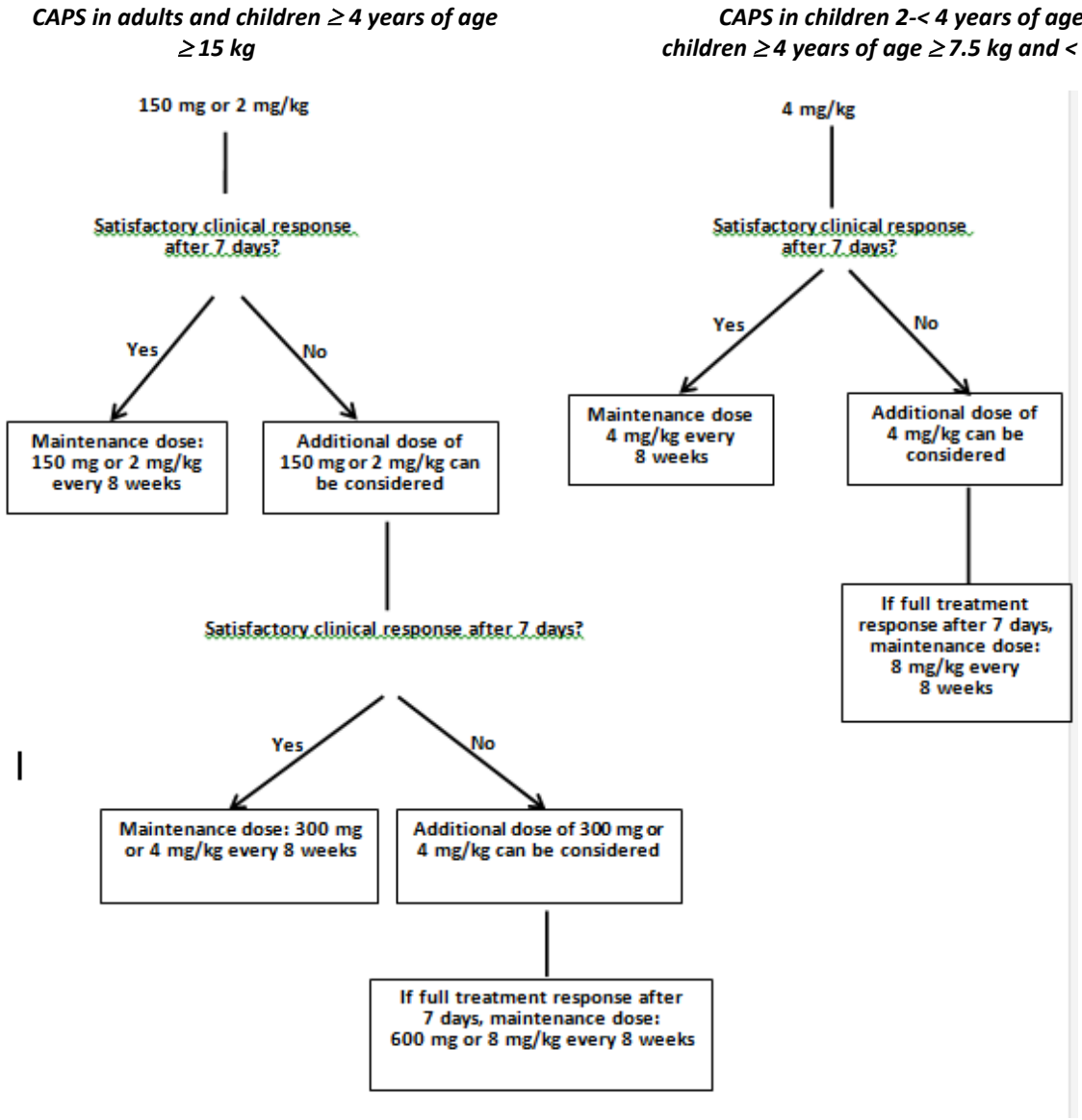
- 4 mg/kg for patients with body weight ≥7.5 kg

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 Ilaris at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg 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 Ilaris 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 Ilaris 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.



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

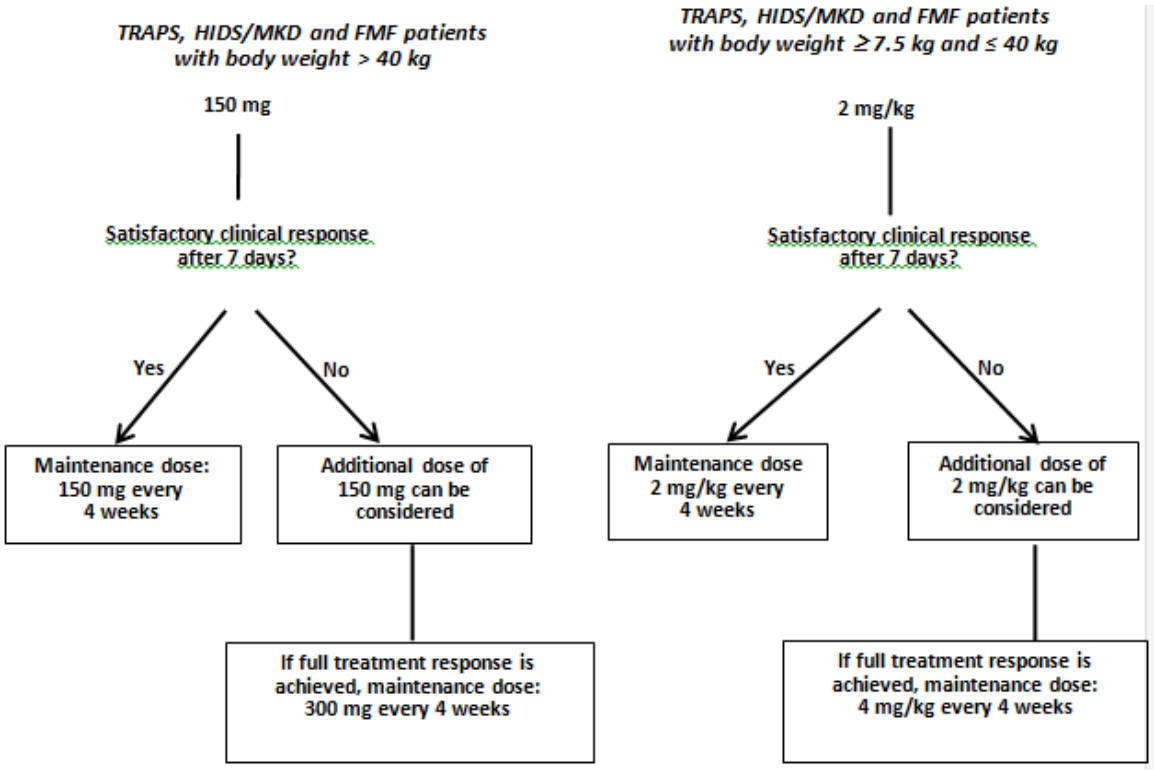
The recommended starting dose of Ilaris in TRAPS, HIDS/MKD and FMF patients is:

- 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 Ilaris at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks should be maintained.

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



SJIA

The recommended dose of Ilaris for SJIA patients with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with Ilaris 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. Ilaris should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of Ilaris for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, Ilaris 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 Ilaris. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of Ilaris may be administered (see section 5.2).

Special populations:

Paediatric population

CAPS, TRAPS, HIDS/MKD and FMF

The safety and efficacy of Ilaris 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 Ilaris in SJIA patients under 2 years of age have not been established (see section 4.1 Therapeutic indications). No recommendation on a posology can be made.

Gouty arthritis

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

Elderly
No dose adjustment is required.

Hepatic impairment
Ilaris has not been studied in patients with hepatic impairment.

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 Ilaris.

Each vial of Ilaris is for a single use in a single patient, for a single dose.
For instructions on use and handling of the reconstituted solution, 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

Infections

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

Treatment of CAPS, TRAPS, HIDS/MKD, FMF and SJIA

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

Treatment of gouty arthritis
Ilaris should not be administered during an active infection.

Concomitant use of Ilaris 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 Ilaris treatment. The causal relationship of Ilaris to these events cannot be excluded.

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 Ilaris without clinical evidence of a latent or active tuberculosis infection.

It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as Ilaris increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g., tuberculin skin test, Interferon-Gamma-Release-Assay or chest X-ray) should be performed in all patients (local recommendations may apply). Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with Ilaris. All patients should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (e.g.

persistent cough, weight loss, subfebrile temperature) appear during Ilaris therapy. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Neutropenia and leukopenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including Ilaris. Treatment with Ilaris should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies

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

Hypersensitivity reactions

Hypersensitivity reactions with Ilaris therapy have been reported. The majority of these events were mild in severity. During clinical development of Ilaris in over 2,600 patients, no anaphylactoid or anaphylactic reactions 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 Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks (see section 4.5).

Prior to initiation of Ilaris 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 SJIA patients

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between Ilaris 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 Ilaris 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 Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of Ilaris treatment, the recommendation is to wait for at least 3 months after the last Ilaris 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 Ilaris 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 Ilaris 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 fetus/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 Ilaris 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 Ilaris 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 Ilaris on human fertility have not been conducted.
Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1beta 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

Over 2,600 subjects including approximately 480 children (aged 2 to 17 years) have been treated with Ilaris in interventional studies in patients with CAPS, TRAPS, HIDS/MKD, FMF, SJIA, gouty arthritis, or other IL-1beta mediated diseases, and healthy volunteers. Serious infections have been observed. 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 Ilaris (see sections 4.3 and 4.4).

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

CAPS

A total of 211 adult and pediatric CAPS patients (including FCAS/FCU, MWS, and NOMID/CINCA) have received Ilaris in clinical trials. The safety of Ilaris compared with placebo was investigated in a pivotal phase III trial that consisted of an 8-week, open-label period (Part I), a 24-week, randomised, double-blind and placebo-controlled withdrawal period (Part II), and a 16-week open-label period on Ilaris (Part III). All patients were treated with Ilaris 150 mg subcutaneous or 2 mg/kg if body weight was ≥15 kg and ≤40 kg.

TRAPS, HIDS/MKD, FMF

A total of 169 adult and paediatric TRAPS, HIDS/MKD and FMF patients aged 2 years and above received Ilaris in one pivotal phase III clinical trial. The safety of Ilaris compared with placebo was investigated in this trial which consisted of a 12-week screening period (Part I), and a 16-week, randomised, double-blind, placebo-controlled treatment period (Part II). Patients treated with Ilaris were treated with 150 mg subcutaneous or 2 mg/kg if body weight was ≤ 40 kg (see section 5.1).

SJIA

A total of 324 SJIA patients aged 2 to < 20 years have received Ilaris in clinical trials, including 293 patients aged 2 to < 16 years old, 21 patients aged 16 to < 18 years old and 10 patients aged 18 to < 20 years old. The safety of Ilaris compared to placebo was investigated in two pivotal Phase III studies (see section 5.1).

Gouty arthritis

More than 700 patients with gouty arthritis have been treated with Ilaris at doses from 10 mg to 300 mg in randomised, double-blind and active-controlled clinical trials of up to 24 weeks' duration. More than 250 patients have been treated with the recommended dose of 150 mg in Phase II and III trials (see section 5.1).

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

Table -1 Tabulated list of adverse reactions in CAPS, TRAPS, HIDS/MKD, FMF, SJIA and gouty arthritis

MedDRA System Organ Class	**All 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

In a subset of young adult SJIA patients aged 16 to 20 years (n=31), the safety profile of Ilaris was consistent with what was observed in SJIA patients less than 16 years of age.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients

During clinical trials with Ilaris 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 Ilaris 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 reductions ≥ Grade 2 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 (≥ 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 program, transient decreased white blood cell (WBC) counts ≤ 0.8× lower limit of normal (LLN) were reported in 33 patients (16. 5%).

In the overall SJIA program, transient decreases in absolute neutrophil count (ANC) to less than $1x10^9$/L were reported in 12 patients (6.0%). In the overall SJIA program, transient decreases in platelet counts (<LLN) were observed in 19 patients (9.5%).

ALT/AST

In the overall SJIA program, 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 Ilaris compared to 1.4% treated with triamcinolone acetonide. Decreases in absolute neutrophil counts (ANC) to less than 1 x 10^9/L were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts < 0.5 x 10^9/L were also observed (see section 4.4).

Mild (< LLN and > 75 x 10^9/L) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with Ilaris 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 Ilaris treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on urate lowering therapy (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 Ilaris -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 Ilaris -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 Ilaris -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 Ilaris and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Paediatric population

There were 80 pediatric CAPS patients (2-17 years of age) who received canakinumab in the studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of Ilaris 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 Ilaris 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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-1beta (IL-1beta) antibody of the IgG1/k isotype. Canakinumab binds with high affinity specifically to human IL-1beta 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 overproduction 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.

SJIA

Systemic juvenile idiopathic arthritis is a severe autoinflammatory disease, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1beta.

Common features of SJIA include fever, rash, hepatosplenomegaly, lymphadenopathy, polyserositis and arthritis. Treatment with canakinumab resulted in a rapid and sustained improvement of both the articular and the systemic features of SJIA with significant reduction of the number of inflamed joints, prompt resolution of fever and reduction of acute phase reactants in the majority of patients (see 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 Ilaris have been demonstrated in patients with varying degrees of disease severity and different CAPS phenotypes (including FCAS/FCU, MWS, and NOMID/CINCA). Only patients with confirmed NLRP3 mutation were included in the pivotal study.

In the Phase I/II study, treatment with Ilaris had a rapid onset of action, with disappearance or clinically significant improvement of symptoms within one day after dosing. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalised rapidly within days of Ilaris 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 Ilaris (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- Part I: A complete clinical and biomarker response to Ilaris (defined as composite of physician's global assessment on autoinflammatory and on skin disease ≤ minimal and CRP or SAA values < 10 mg/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 Ilaris 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 Ilaris 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)			
	Ilaris 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.

Paediatric population

The CAPS trials with Ilaris 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 Ilaris 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 Ilaris 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 Ilaris 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 Ilaris (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 Ilaris 150 mg (2 mg/kg for patients ≤ 40 kg) s.c. or placebo every 8 weeks.
- Part IV: All Part III patients treated with Ilaris 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 ≥ 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, Ilaris was superior to placebo for all three disease cohorts. Ilaris 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 Ilaris 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)			
	Ilaris 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 Ilaris 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).

SJIA
The efficacy of Ilaris for the treatment of active SJIA was assessed in two pivotal 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 Ilaris in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) Ilaris 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. Ilaris 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	
	Ilaris N=43	Placebo N=41	Ilaris N=43	Placebo N=41
ACR30	84%	10%	81%	10%
ACR50	67%	5%	79%	5%
ACR70	61%	2%	67%	2%
ACR90	42%	0%	47%	2%
ACR100	33%	0%	33%	2%
Inactive disease	33%	0%	30%	0%
Treatment difference for all ACR scores was 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 Ilaris (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 Ilaris (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among Ilaris treated patients was consistent at day 29.

Study G2301
Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by Ilaris. 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) Ilaris administered every 4 weeks for up to 32 weeks. Patients in Part II (double-blind) received either Ilaris 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 Ilaris 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 Ilaris 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 Ilaris 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 Ilaris 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 Ilaris 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).

The efficacy observed in the studies G2305 and G2301 was maintained in the ongoing, open-label long-term extension study (data available through median of 49 weeks of follow-up). In this study, 25 patients who had a strong ACR response for a minimum of 5 months reduced their Ilaris dose to 2 mg/kg every 4 weeks and maintained a paediatric ACR100 response throughout the time the reduced dose was given (median 32 weeks, 8-124 weeks).

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

SJIA in young adults
Efficacy of Ilaris in a subset of young adult SJIA patients aged 16 to 20 years was consistent with the efficacy observed for patients less than 16 years of age.

Gouty arthritis
The efficacy of Ilaris 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 Ilaris 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 Ilaris 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 Ilaris 150 mg compared with triamcinolone acetonide at 72 hours. Ilaris 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 Ilaris 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 Ilaris in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)

In clinical studies, Ilaris 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 Ilaris were observed in approximately 1.5%, 3% and 2% of the patients treated with Ilaris 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 Ilaris observed in TRAPS, HIDS/MKD and FMF patients treated with doses of 150 mg and 300 mg over 16 weeks of treatment.

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 µg/ml and 708 µg*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 µg/ml, 24.3 µg/ml, 767 µg*d/ml) compared to the weight categories < 40 kg (4.0 µg/ml, 19.9 µg/ml, 566 µg*d/ml) and > 70 kg (4.6 µg/ml, 17.8 µg/ml, 545 µg*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/day in a CAPS patient of body weight 70 kg and 0.11 L/day 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 ± 6.6 µg/ml. The estimated steady state AUC_{tau} was 636.7 ± 260.2 µg*d/ml.

SJIA

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.

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 (±SD) for $C_{min,ss}$, $C_{max,ss}$ and $AUC_{,ss4w}$ were 14.7±8.8 µg/ml, 36.5 ± 14.9 µg/ml and 696.1 ± 326.5 µg*d/ml, respectively.

The AUC_{ss4w} in each age group was, 615, 707 and 742 µg*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 µg/ml) and AUC_{ss} (594 vs 880 µg*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 µg/ml and AUC_{inf}: 495 µg*d/ml) was lower than in a typical 70 kg CAPS patient (15.9 µg/ml and 708 µg*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 cross-reactivity, repeated dose, immunotoxicity, reproductive and juvenile toxicity studies performed with canakinumab or a murine anti-murine IL-1 beta antibody.

Since canakinumab binds to marmoset (*C. jacchus*) and human IL-1 beta with a similar affinity, the safety of canakinumab has been studied in the marmoset. No undesirable effects of canakinumab were seen following twice weekly administration to marmosets for up to 26 weeks or in an embryofoetal developmental toxicity study in pregnant marmosets. Plasma concentrations that are well tolerated in animals are in excess of at least 42-fold (C_{max}) and 78-fold (C_{avg}) the plasma concentrations in paediatric CAPS patients (body weight 10 kg) treated with clinical doses of canakinumab up to 8 mg/kg subcutaneously every 8 weeks. Plasma concentrations that are well tolerated in animals exceed at least 62-fold (C_{max}) and 104-fold (C_{avg}) the plasma concentrations in paediatric SJIA patients, treated with up to 4 mg/kg via the subcutaneous route every 4 weeks. In addition, no antibodies to canakinumab were detected in these studies. No non-specific tissue cross-reactivity was demonstrated when canakinumab

was applied to normal human tissues.

Formal carcinogenicity studies have not been conducted with canakinumab.

In an embryofoetal development study in marmosets canakinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis.
No undesirable effects of a murine anti-murine IL-1 beta antibody were seen in a complete set of reproductive and juvenile studies in mice. Anti-murine IL-1 beta did not elicit adverse events on foetal or neonatal growth when administered throughout late gestation, delivery and nursing (see section 4.6). The high dose used in these studies was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity.
An immunotoxicology study in mice with a murine anti-murine IL-1 beta antibody showed that neutralising IL-1 beta has no effects on immune parameters and caused no impairment of immune function in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose 92.35 mg per vial

L-Histidine
L-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

The expiry date of the product is printed on the package materials.

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

150 mg of 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 (1X4) 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. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for reconstitution

Using aseptic technique, reconstitute each vial of Ilaris 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 1.0 ml) and subcutaneously inject using a 27 G x 0.5 inch (13 mm) needle.

Disposal

The healthcare professional should dispose of, by appropriate procedure, the vials, syringes and needles in accordance with local requirements.

7. Manufacturer:

Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

8. Registration Holder:

Novartis Israel Ltd., 36 Shacham St., Petach-Tikva.

Registration Number:

144 60 32964