AUSTRALIAN PRODUCT INFORMATION – ILARIS (canakinumab (*rmc*)) Powder for solution for injection and Solution for injection

1 NAME OF THE MEDICINE

Active ingredient: Canakinumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Canakinumab is a high-affinity human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine myeloma SP2/0 cell line.

Powder for solution for injection
Ilaris is a sterile, white, lyophilised powder that is reconstituted with water for injections and administered as a subcutaneous (SC) injection. A reconstituted single-use vial delivers 150 mg canakinumab per 1 mL.

Excipients: Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, dilute hydrochloric acid.

Solution for injection
Ilaris is a colourless to slightly brownish yellow solution, in a 2 mL colourless glass vial with grey rubber stopper and green flip off cap and administered as a SC injection.

Excipients: Mannitol, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, water for injection.

3 PHARMACEUTICAL FORM

Powder for solution for injection

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Ilaris is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years or older.

4.2 Dose and method of administration

Dosage for CAPS:

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of CAPS.

The recommended starting dose of Ilaris for CAPS patients is:
Adults and children ≥4 years of age:

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

Children 2 to <4 years of age:

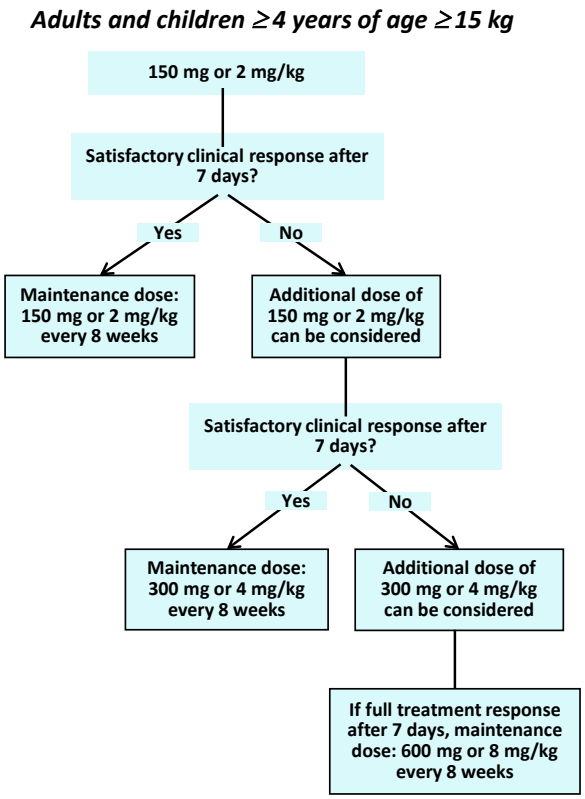
- 4 mg/kg for patients with body weight ≥7.5 kg

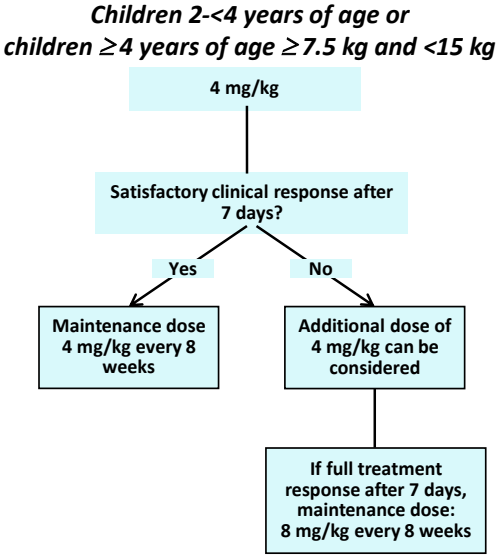
This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2mg/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.

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.

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





Dosage for sJIA:

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of sJIA.

The recommended dose of Ilaris for sJIA patients with body weight ≥7.5 kg is 4 mg/kg (up to maximum of 300 mg) administered every four weeks via subcutaneous injection. The treating physician should consider whether patients without clinical improvement should continue treatment with Ilaris.

Method of Administration

Subcutaneous injection.

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

Instructions for Use and Handling (powder for solution for injection)

Reconstitute each vial of Ilaris by slowly injecting 1.0 mL water for injections with a 1 mL syringe and a 18 G x 2" needle. Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for 5 minutes. Then gently turn the vial upside down and back again ten times. If possible, avoid touching the rubber stopper with your fingers. Allow to stand for about 15 minutes at room temperature to obtain a clear 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 essentially free of visible particles and clear to opalescent. The solution should be colourless or may have a slightly brownish-yellow tint. If not used within 60 minutes of reconstitution, the solution should be stored in the refrigerator (2°C to 8°C) and used within 24 hours.

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

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

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

Instructions for Use and Handling (solution for injection)

Ilaris 150 mg/1 mL solution for injection is supplied in a single-use vial for individual use. Any unused product or waste material should be disposed of in accordance with local requirements.

Let the vial stand unopened for 10 minutes to allow the contents to reach room temperature. Do not expose the vial to heat. The solution should be clear to opalescent and colourless or may have a slight brownish-yellow tint. Do not use if particles are present in the solution.

Carefully withdraw the required volume depending on the dose to be administered using an appropriate size needle and a 1 ml syringe and subcutaneously inject using a 27 G x 0.5" needle. Once the vial is pierced, use the solution immediately.

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

4.3 Contraindications

Confirmed hypersensitivity to the active substance or to any of the excipients (see section 4.4 Precautions and section 4.8 Adverse Effects).

4.4 Special warnings and precautions for use

Infections

Ilaris is associated with an increased incidence of serious infections. Physicians should exercise caution when administering Ilaris to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Treatment with Ilaris should not be initiated or continued in patients with active infection requiring medical intervention.

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

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

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

It is unknown whether the use of IL-1 inhibitors such as Ilaris increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history and appropriate screening tests. Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with Ilaris. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Malignancies

Malignancy events have been reported in patients treated with Ilaris. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown. A potential risk cannot be excluded in patients treated with Ilaris.

Hypersensitivity Reactions

Hypersensitivity reactions with Ilaris therapy have been reported. The majority of these events were mild in severity. During clinical development of Ilaris, no anaphylactoid or anaphylactic reactions have been reported. However, the risk for severe hypersensitivity reactions, which is not uncommon for injectable proteins, can not be excluded (see section 4.3 Contraindications and section 4.8 Adverse Effects).

Vaccinations

Live vaccines should not be given concurrently with Ilaris (see section 4.5 Interactions with Other Medicines).

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 (see section 4.8 Adverse Effects). 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.

Use in hepatic impairment

No dose adjustment is needed in patients with hepatic impairment. Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8 Adverse Effects).

Macrophage activation syndrome (in sJIA patients)

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA, and should be aggressively treated.

Physicians should be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for MAS. Based on clinical trial experience, ILARIS does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be made.

Use in renal impairment

Ilaris has not been studied in patients with renal impairment. However, clinical experience in such patients is limited.

Use in the elderly

No dose adjustment is required in geriatric patients. However, clinical experience in such patients is limited.

Paediatric use

Ilaris is not indicated for use in children below age 2 years or with body weight below 7.5 kg. The safety and efficacy of ILARIS in CAPS patients under two years of age have not been established. Limited data on CAPS patients under two years are available (see section 5.2 Pharmacokinetics in children).

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

Effects on laboratory tests

Haematology:
During clinical trials with canakinumab mean values for haemoglobin increased and decreased for white blood cell, neutrophils and platelets.

Hepatic transaminases:
Elevations of transaminases have been observed rarely in CAPS patients.

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

Immunogenicity

No anaphylactic reactions were observed in patients treated with Ilaris.

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

4.5 Interactions with other medicines and other forms of interactions

Interactions between Ilaris and other medicinal products, including combinations with other biologics such as tocilizumab, have not been investigated in formal studies.

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1 beta. Thus, CYP450 expression may be normalised when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted.

On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

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

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Ilaris. Therefore, live vaccines should not be given concurrently with Ilaris. It is recommended that, if possible, paediatric and adult patients should complete all immunisations in accordance with current immunisation guidelines prior to initiating Ilaris therapy.

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

Limited data suggests that vaccination with non-live, standard of care childhood vaccinations results in protective levels of antibody.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Canakinumab had no effect on sperm motility and morphology in male marmoset (*C. jacchus*) at SC doses up to 269 times the clinical dose based on AUC. A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice. The high dose (150 mg/kg) in the mouse study was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity.

Use in pregnancy – Pregnancy Category B3

There are no adequate and well-controlled studies of canakinumab in pregnant women or women of child-bearing potential. The risk for the foetus or mother is unknown because animal reproduction studies are not always predictive of the human response. Canakinumab should be given to a pregnant woman only if clearly needed.

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

Animal data
Studies on embryofoetal development were performed in marmoset monkeys dosed with canakinumab and in mice dosed with a murine anti-murine IL-1 beta antibody. There was no evidence of maternal toxicity, embryo-toxicity or teratogenicity. In addition, canakinumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation. Pregnant marmosets dosed with canakinumab subcutaneously at doses of 15, 50 or

150 mg/kg twice weekly (30 to 306 times the human dose based on AUC) during organogenesis (gestation days 25 to 109) showed an increase in the incidence of incomplete ossification, misalignment and/or bipartite of the terminal caudal vertebra in fetuses at all dose levels.

No undesirable effects of a murine anti-murine IL-1 beta antibody were seen in a complete set of reproductive studies in mice. In addition, no effects on labor and delivery were observed. The high dose used in these studies was in excess of the maximally effective dose in terms of IL-1 beta suppression and activity. In mice subcutaneously administered the murine anti-murine IL-1 beta antibody at doses of 15, 50 or 150 mg/kg on gestation days 6, 11 and 17, the incidence of incomplete ossification of the parietal and frontal skull bones of fetuses was increased at all dose levels.

Use in lactation

It is not known whether canakinumab is transferred into breast milk. There are no data on the effects of Ilaris on the breastfed child or milk production. Breast-feeding is not recommended during Ilaris therapy.

In a mouse study, a murine anti-murine IL-l beta antibody at up to 150 mg/kg SC weekly administered to the dam during gestation and lactation had no effects on pup development. High serum levels of the antibody were detected in the pups.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

In blinded and open-label clinical trials in patients with CAPS and sJIA, the most frequently reported adverse drug reactions were infections predominantly of the upper respiratory tract. The majority of the events were mild to moderate although serious infections were observed. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.

Hypersensitivity reactions have been reported in patients treated with Ilaris in clinical trials (see section 4.3 Contraindications and section 4.4 Precautions).

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

CAPS

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

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

	Phase III trial			
	Part I	Part II		Part III
	Canakinumab N=35 (n%)	Canakinumab N=15 (n%)	Placebo N=16 (n%)	Canakinumab N=31 (n%)
Infections and infestations				
Nasopharyngitis	4 (11.4%)	5 (33.3%)	3 (18.8%)	4 (12.9%)
Urinary tract infection	0	2 (13.3%)	0	1 (3.2%)
Upper respiratory tract infection	1 (2.9%)	1 (6.7%)	1 (6.3%)	1 (3.2%)
Viral infection	3 (8.6%)	2 (13.3%)	3 (18.7%)	1 (3.2%)
General disorders and administration site conditions				
Injection site reaction	3 (8.6%)	2 (13.4%)	1 (6.3%)	1 (3.2%)
Nervous system disorders				
Dizziness/vertigo	3 (8.6%)	0	0	3 (9.7%)

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

Paediatric Population

There were 80 paediatric patients with an age range from 2 years to 17 years in the CAPS studies. Overall, there were no clinically meaningful differences for 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. However, the risk of infection in younger children (aged <11 years) is higher than in older children and adolescents. 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.

sJIA

A total of 201 sJIA patients aged 2 to <20 years have received Ilaris in clinical trials. The safety of Ilaris compared to placebo was investigated in two pivotal phase III studies (see section 5.1 Clinical trials).

Adverse reactions are listed according to MedDRA version 15.0 system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency category with the most common first. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

	G2301			G2305		Frequency category
	Part I	Part II				
	Ilaris N=177	Ilaris N=50	Placebo N=50	Ilaris N=43	Placebo N=41	

	(n %)	(n %)	(n %)	(n %)	(n %)	
Infections and infestations						
Infection (e.g. nasopharyngitis, (viral) upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)	97 (54.8%)	27 (54%)	19 (38%)	13 (30.2%)	5 (12.2%)	Very common
Gastrointestinal disorders						
Abdominal pain (upper)	25 (14.1%)	8 (16%)	6 (12%)	3 (7%)	1 (2.4%)	Very common
General disorders and administration site conditions						
Injection site reaction*						
mild	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)	Very common
moderate	2 (1.1%)	1 (2.0%)	0	0	0	Common

* No injection site reaction led to study discontinuation

Laboratory abnormalities (in sJIA)

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

Transient decreases in absolute neutrophils counts (ANC) to less than $1x10^9$/L were reported in 3 patients (6.0%) in the Ilaris group compared to 1 patient (2.0%) in the placebo group. One case of ANC counts <$0.5x10^9$/L was observed in the Ilaris group and none in the placebo group (see section 4.4 Precautions).

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

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

4.9 Overdose

There is limited experience with overdosage. In case of overdosage, it is recommended that the patient be monitored for any signs and symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted as necessary.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group, ATC
Interleukin inhibitors; ATC code: L04AC08.

5.1 Pharmacodynamic properties

Mechanism of action

Canakinumab is a human monoclonal anti-human interleukin-1beta (IL-1beta) antibody of the IgG1/kappa isotype. Canakinumab binds with high affinity to human IL-1beta and neutralises the biological activity of human IL-1beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1beta-induced gene activation and the production of inflammatory mediators such as interleukin-6 or cyclooxygenase-2. Canakinumab is therefore suited to treat diseases and pathologies characterised by local or systemic overproduction of IL-1beta.

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

CAPS
Cryopyrin-Associated Periodic Syndromes (CAPS) patients who have uncontrolled overproduction of IL-1beta (manifest as fever, fatigue, skin rash, arthritis, intense leukocytosis, high platelet count, and acute phase protein elevation) show a rapid response to therapy with canakinumab. Following canakinumab treatment, CRP and SAA levels, leukocytosis and high platelet count rapidly returned to normal.

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

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 Trials).

Clinical trials

CAPS

The efficacy and safety of canakinumab have been demonstrated in patients with varying degrees of disease severity and different CAPS phenotypes including:

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

In the Phase I/II study, treatment with canakinumab had a rapid onset, 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. a 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 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 ≤ minimal and CRP or SAA values <10 mg/L) was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms and patient's assessment of symptoms.

- Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as disease relapse/flare: none (0%) of the patients randomised to canakinumab flared, compared with 81% of the patients randomised to placebo.

- Part III: Patients treated with placebo in Part II who entered the open-label extension on canakinumab, again showed a significant clinical and serological improvement of disease activity, comparable to patients continuously treated with canakinumab.

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 (n=185), 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Fewer patients aged 2 to <4 years achieved complete response (57.1%) than older pediatric and adult patients. Of the patients who had achieved a complete response, 89.3% maintained response without relapsing.

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

The CAPS trials with canakinumab included a total of 80 paediatric patients with an age range from 2 to 17 years. Overall, there were no clinically meaningful differences for the efficacy, safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211). The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

Limited data suggests that vaccination with non-live, standard of care childhood vaccinations results in protective levels of antibody..

sJIA

The efficacy of Ilaris for the treatment of active sJIA was assessed in two pivotal phase III studies (G2305 and G2301). Patients enrolled were aged 2 to <20 years (mean age at baseline: 8.5 years) with a confirmed diagnosis of sJIA at least 2 months before enrolment (mean disease duration at

baseline: 3.5 years). Patients had active disease defined as ≥2 joints with active arthritis (mean number of active joints at baseline: 15.4), documented spiking, intermittent fever (body temperature >38°C) for at least 1 day within 1 week before study drug administration, and CRP >30 mg/L (normal range <10 mg/L) (mean CRP at baseline: 200.5 mg/L). Patients were allowed to continue their stable dose of methotrexate, corticosteroids, and/or NSAIDs without change, except for tapering of the corticosteroid dose as per study design in Study G2301.

Study G2305

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

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

All primary and secondary endpoints were met. Percentage of patients by paediatric ACR response and inactive disease are presented in Table 3.

Table 3. 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 p≤0.0001 and not available for inactive disease.

Ilaris treatment improved components of paediatric ACR core set as compared to placebo at Days 15 and 29 (Table 4). All patients treated with Ilaris had no fever at Day 3 compared to 86.8% of patients treated with placebo (p=0.0098).

Table 4. Median value (median percent change from baseline) at days 15 and 29 for paediatric ACR core components and pain

Pediatric ACR component	Baseline		Day 15		Day 29	
	ILARIS N=43	Placebo N=41	ILARIS N=43	Placebo N=25	ILARIS N=38*	Placebo N=7
Joints with active arthritis	10	7	2 (-67%)	9 (0%)	1 (-86%)	4 (-32%)
Joints with limited range of motion	8	6	2 (-73%)	8 (0%)	2 (-83%)	2 (-33%)
CRP (mg/L)	141	137	10 (-91%)	99 (5%)	12 (-91%)	81 (-13%)
CHAQ disability score	1.63	1.50	0.63 (-68%)	1.63 (-11%)	0.19 (-85%)	1.5 (20%)
Physician global assessment of disease activity VAS (mm)	67	66	20 (-69%)	56 (-5%)	11 (-83%)	28 (-38%)
Parent/patient global assessment of overall wellbeing VAS (mm)	63	61	15 (-73%)	65 (1%)	7 (-91%)	60 (-17%)
Patient pain score VAS (mm)	73	67	8 (-87%)	66 (15%)	7 (-89%)	56 (-12%)

VAS – Visual analog scale (0-100 mm)

A negative value indicates improvement compared to baseline

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

No patient in study G2305 discontinued because of an adverse event.

Study G2301

Study G2301 was a randomized, double-blind, placebo-controlled withdrawal study of flare prevention by Ilaris in patients with active sJIA. Flare events were defined as reappearance of fever >38°C for at least 2 consecutive days not due to infections and/or all JIA paediatric flare criteria (≥30% worsening in at least 3 of 6 response variables; not more than 1 of 6 response variable improving by ≥30%; ≥20 mm VAS for overall well-being if physician or parent global assessment is measured; worsening in ≥2 joints; CRP >30 mg/L).

The study consisted of two major parts with two independent primary endpoints. 177 patients were enrolled in the study and received 4mg/kg s.c. Ilaris every 4 weeks for up to 32 weeks (median 16 weeks) in Part I, and either s.c. Ilaris 4mg/kg or placebo every 4 weeks in Part II. The study was stopped when the 37 flare events had occurred in Part II.

In Part I, a total of 77/177 patients (44%) discontinued the study, with the most frequently reported reasons being a lack of response to therapy by day 29 (34 patients, 19%) or inability to successfully reduce their corticosteroid dose (24 patients, 14%). A total of 48 of the 77 patients who discontinued in Part I enrolled into a long term extension trial to continue treatment with Ilaris.

Corticosteroid dose tapering:

Part I had an open-label design to assess whether Ilaris allowed successful tapering of corticosteroids in at least 25% of the patients entering the study using a corticosteroid. The primary endpoint of Part I was met. Of the 128 patients who entered the study taking corticosteroids, 57 (45%) successfully tapered the corticosteroid dose ($p<0.0001$) and 42 (33%) discontinued their corticosteroids. Of the 92 patients who attempted corticosteroid tapering, 57 (62%) successfully tapered the corticosteroid dose, 42 (46%) discontinued corticosteroids, 24 (26%) patients still on corticosteroids had the dose reduced to ≤0.2mg/kg/day (prednisone

equivalent). Successful corticosteroid dose taperers reduced their mean corticosteroid dose from 0.34 mg/kg/day prednisone equivalent at baseline to 0.05mg/kg/day representing a mean 90% dose reduction. For patients attempting corticosteroid dose reduction who entered with a prednisone equivalent dose of ≥0.5mg/kg/day (N=28), 15 (54%) had their dose reduced by at least 0.3mg/kg which resulted in a prednisone equivalent dose of ≤0.5mg/kg/day, including 7 (25%) who discontinued corticosteroids.

Time to flare:

Part II was an event-driven withdrawal design to demonstrate that the time to flare was longer with Ilaris than with placebo. The primary endpoint of Part II was met after a median duration to flare of 31.6 weeks with canakinumab and 23.4 weeks with placebo. The probability of experiencing a flare in Part II was statistically lower for the Ilaris treatment group than for the placebo group. The median time to flare was 236 days for the placebo group and could not be determined for the Ilaris group because less than 50% of the patients treated with Ilaris experienced a flare event over the observation period (maximum of > 80 weeks). This corresponded to a statistically significant 64% relative reduced risk for patients in the Ilaris group to experience a flare event as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032).

In Part II, 37 patients discontinued the study: 11/50 patients on canakinumab and 20/50 patients on placebo discontinued due to unsatisfactory therapeutic effect which occurred between day 113 and day 398. Four patients on placebo and none (0) on canakinumab discontinued due to an adverse event.

Paediatric adapted ACR response and paediatric ACR core components:

Improvements in the paediatric ACR responses and in each of the paediatric ACR core components observed in Study G2305 (Table 3 and Table 4) were similarly observed during open-label Ilaris treatment in Part I of G2301.

Nearly all (139/141, 98.6%) the patients treated with ILARIS had no fever at Day 3.
In 46 of the 120 patients (38.3%) who entered the study with a low haemoglobin the level had increased to within the normal range at their last visit of Part I.

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

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

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

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

Long-term data

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

At the time of the interim results, 25 patients who had a strong ACR response for a minimum of 5 months reduced their Ilaris doe to 2 mg/kg every 4 weeks and maintained a paediatric ACR 100 response throughout the time the reduced dose was given (median 32 weeks, range 8-124 weeks).

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

Incidence of Macrophage Activation Syndrome (MAS)

Eleven cases of MAS were observed in 201 sJIA patients treated with canakinumab in clinical trials (see section 4.4 Precautions).

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Canakinumab binds to serum IL-1β. The distribution volume (Vss) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg, 3.2 litres in a SJIA patient of body weight 33 kg. The expected accumulation ratio was 1.3-fold and 1.6-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks and 4 mg/kg every 4 weeks respectively (see section 4.2 Dosage and administration).

Excretion

The clearance (CL) of canakinumab varied according to body weight and were 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.

Pharmacokinetics in children:

Peak concentrations of canakinumab occurred between 2 to 7 days 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 PK modeling analysis, the pharmacokinetics of canakinumab in children 2 to <4 years of age were similar to patients 4 years of age and older. 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. Pharmacokinetic properties are similar in CAPS and sJIA paediatric populations.

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

5.3 Preclinical safety data

Genotoxicity

Genotoxicity studies have not been conducted with canakinumab.

Carcinogenicity

Carcinogenicity studies have not been conducted with canakinumab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refer to Section 2 - Qualitative and quantitative composition.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2° to 8°C. Refrigerate. Do not freeze. Protect from light.

6.5 Nature and contents of container

Powder for solution for injection: packs containing 1 or 4 vials of 150 mg sterile, lyophilised powder.

Solution for injection: 1 vial of 150 mg/mL solution for injection.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

Structure: Canakinumab comprises two 447(or 448)-residue heavy chains and two 214-residue light chains.

Molecular weight: Approximately 145.157kDa

Chemical name: Immunoglobulin G1, anti-(human interleukin-1beta (IL-1β)) human monoclonal ACZ885; (1Glu>Glp)-γ1 heavy chain (221-214')-disulfide with kappa light chain, dimer (227-227":230-230")-bisdisulfide

CAS number

402710-25-2 (variable heavy γ1 chain)

402710-27-4 (variable light κ chain)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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® = Registered Trademark

9 DATE OF FIRST APPROVAL

10 May 2010

10 DATE OF REVISION

3 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 6.5	Removal of statements relating to deregistered pre-filled syringe/pen and composite pack