

NEW ZEALAND DATA SHEET

ILARIS[®] canakinumab

NAME OF THE MEDICINE

Active ingredient:	Canakinumab
Chemical name:	Immunoglobulin G1, anti-(human interleukin-1beta (IL-1 β)) human monoclonal ACZ885; (1Glu>Glp)- γ 1 heavy chain (221-214')-disulfide with kappa light chain, dimer (227-227'':230-230'')-bisdisulfide
CAS number:	402710-25-2 (variable heavy γ 1 chain) 402710-27-4 (variable light κ chain)
Molecular weight:	Approximately 145.157kDa
Structure:	Canakinumab comprises two 447(or 448)-residue heavy chains and two 214-residue light chains.

DESCRIPTION

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

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, histidine, histidine hydrochloride monohydrate, polysorbate 80, dilute hydrochloric acid.

PHARMACOLOGY

Pharmacotherapeutic group: Interleukin inhibitors; ATC code: L04AC08

Pharmacodynamics

Canakinumab is a fully 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. Cryopyrin-Associated Periodic Syndromes (CAPS) patients who have uncontrolled overproduction of IL-1beta manifest in 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.

Pharmacokinetics

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, the absolute bioavailability of subcutaneous administration of canakinumab was estimated to be 70%. The clearance (CL) and distribution volume (V_{ss}) of canakinumab varied according to body weight and were estimated to be 0.174 L/day and 6.01 l, respectively, in a typical CAPS patient of body weight 70 kg. The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks. 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 300 mg as subcutaneous injection. 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. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults.

CLINICAL TRIALS

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 \leq minimal and CRP or SAA values <10 mg/L) to canakinumab was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms and patient's assessment of symptoms.
- Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as disease relapse/flare: none (0%) of the patients randomized to canakinumab flared, compared with 81% of the patients randomized 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.

Sustained efficacy for more than three years was observed for the initial four patients with continued administration of canakinumab.

No antibodies to canakinumab have been detected in CAPS patients treated with canakinumab.

Experience from individual patients who have received up-titration doses of maximum 300 mg (4 mg/kg for patients ≥ 15 kg and ≤ 40 kg) suggest 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).

The CAPS trials with canakinumab included a total of 15 paediatric patients with an age range from 4 to 17 years (seven adolescents treated with 150 mg, and eight children ≥ 15 kg and ≤ 40 kg treated with 2 mg/kg). Overall, the efficacy, safety and tolerability profile of canakinumab in paediatric patients was comparable to adult patients.

INDICATIONS

Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children aged 4 years and older including:

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

CONTRAINDICATIONS

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

PRECAUTIONS

Serious Infections

Ilaris may be 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 continued or initiated 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. No unusual or opportunistic infections were reported with Ilaris.

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

Immunosuppression

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

Cases suggestive of hypersensitivity reactions with Ilaris therapy have been reported in clinical trials. The majority of these events were mild in severity. 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 ‘Contraindications’ and ‘Adverse effects’).

Vaccinations

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

Use in Pregnancy (Category B3)

There are no adequate and well-controlled studies of canakinumab in pregnant women.

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 teratogenicity. 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. 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.

The risk for the foetus 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.

Use in Lactation

It is not known whether canakinumab is excreted in human milk. Breast-feeding is not recommended during Ilaris therapy.

In a mouse study, a murine anti-murine IL-1 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.

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with canakinumab.

Interactions with Other Medicines

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

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

normalised when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

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

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

Effects on Laboratory Tests

Haematology

During clinical trials with canakinumab mean values for hemoglobin increased and decreased for white blood cell, neutrophils and platelets. These changes were potentially due to a decrease in inflammation and not considered to be of clinical relevance.

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.

ADVERSE EFFECTS

Approximately 700 subjects have been treated with Ilaris in blinded and open-label clinical trials in patients with CAPS, patients with other diseases, and healthy volunteers. A total of 15 serious, suspected drug-related adverse reactions were reported during the clinical programme. The most frequently reported adverse drug reactions in CAPS patients included upper respiratory tract infections and nasopharyngitis across all CAPS studies. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.

A total of 78 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). 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	
	Canakinumab n=35	Canakinumab n=15	Placebo n=16
Infections and infestations			
Nasopharyngitis	4 (11.4%)	5 (33.3%)	3 (18.8%)
Urinary tract infection	0	2 (13.3%)	0
Upper respiratory tract infection	1 (2.9%)	1 (6.7%)	1 (6.3%)
Viral infection	3 (8.6%)	2 (13.3%)	3 (18.7%)
Skin and subcutaneous tissue disorders			
Injection site reaction	3 (8.6%)	2 (13.4%)	1 (6.3%)

Vertigo has been reported in 6 to 13% of patients in CAPS studies and reported as serious in a few cases. All events resolved despite continued treatment with Ilaris.

Cases suggestive of hypersensitivity reactions with Ilaris therapy have been reported in patients treated with canakinumab in clinical trials. The majority of these events were mild in severity. No anaphylactoid or anaphylactic reactions have been reported (see ‘Contraindications’ and ‘Precautions’).

Paediatric Population

Fifteen paediatric CAPS patients (4 to 17 years of age) demonstrated similar efficacy and safety to adult patients. Specifically, the overall frequency and severity of infectious episodes in paediatric patients were comparable to that in the adult population. Infection of the upper respiratory tract was the most frequently reported infection.

DOSAGE AND ADMINISTRATION

The recommended dose of Ilaris is 150 mg for CAPS patients with body weight >40 kg, and 2 mg/kg for CAPS patients with body weight ≥ 15 kg and ≤ 40 kg.

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

Renal and Hepatic Impairment

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

Ilaris has not been studied in patients with hepatic impairment.

Paediatric Patients

Ilaris is not recommended for use in children below age 4 years or with body weight below 15 kg due to a lack of clinical data.

Geriatric Patients

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

Method of Administration

Subcutaneous injection.

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

Instructions for Use and Handling

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. If not used within 60 minutes of reconstitution, the solution should be stored in the refrigerator (2°C to 8°C) and used within 24 hours.

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

Injection into scar-tissue should be avoided as this may result 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

OVERDOSAGE

No case of overdose has been reported.

PRESENTATION AND STORAGE CONDITIONS

Ilaris is supplied as a pack containing 1 or 4 single-use vial of 150 mg sterile, lyophilised powder.

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

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MEDICINE CLASSIFICATION

Prescription Medicine

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