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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ILARIS safely and effectively. See full prescribing information for ILARIS

ILARIS (canakinumab)

Injection for Subcutaneous use
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

ILARIS is an interleukin-1β blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS) (1)

----------DOSAGE AND ADMINISTRATION----------

150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Sterile, single-use 6-mL, glass vial containing 180 mg of ILARIS as a lyophilized powder for reconstitution. (3)

----------CONTRAINDICATIONS----------

Confirmed hypersensitivity to the active substance or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interleukin-1 blockade may interfere with immune response to infections. Treatment with medications that work through inhibition of IL-1 has been associated with an increased risk of serious infections. ILARIS has been 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. Discontinue treatment with ILARIS if a patient develops a serious infection. Do not administer ILARIS to patients during an active infection requiring medical intervention. (5.1)
- Live vaccines should not be given concurrently with ILARIS. Prior to initiation of therapy with ILARIS, patients should receive all recommended vaccinations. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported by patients with CAPS treated with ILARIS are nasopharyngitis, diarrhea, influenza, headache and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

No formal drug interaction studies have been conducted with ILARIS.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No Human data. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ILARIS (canakinumab) is an interleukin-1β blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INJECTION FOR SUBCUTANEOUS USE ONLY.

2.2 Recommended Dose

The recommended dose of ILARIS is 150 mg for CAPS patients with body weight greater than 40 kg. For CAPS patients with body weight between 15 kg and 40 kg, the recommended dose is 2 mg/kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg.

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

2.3 Preparation for Administration

Using aseptic technique, reconstitute each vial of ILARIS by slowly injecting 1 mL of preservative-free Sterile Water for Injection with a 1 mL syringe and an 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. 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 particulate matter is present in the solution. Tap the side of the vial to remove any residual liquid from the stopper. The reconstituted solution should be essentially free from particulates, and clear to opalescent. The solution should be colorless or may have a slight brownish-yellow tint. If the solution has a distinctly brown discoloration it should not be used. If not used within 60 minutes of reconstitution, the solution should be stored in the refrigerator at 2 to 8° C (36 to 46° F) and used within 4 hours. Slight foaming of the product upon reconstitution is not unusual.

Using a sterile syringe and needle carefully withdraw the required volume depending on the dose to be administered (0.2 mL to 1 mL) and subcutaneously inject using a 27 G x 0.5” needle.

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

ILARIS 180-mg powder for solution for injection is supplied in a single-use vial. Any unused product or waste material should be disposed of in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

ILARIS is supplied as a 180 mg white lyophilized powder for solution for subcutaneous injection. Reconstitution with 1 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug, resulting in a total volume of 1.2 mL reconstituted solution. The reconstituted ILARIS is a clear to slightly opalescent, colorless to a slight brownish yellow tint, essentially free from particulates, 150 mg/mL solution.

4 CONTRAINDICATIONS

Confirmed hypersensitivity to the active substance or to any of the excipients [*see Warnings and Precautions (5.3) and Adverse Reactions (6.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

ILARIS may be associated with an increased risk 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. ILARIS should not be administered to patients during an active infection requiring medical intervention. Administration of ILARIS should be discontinued if a patient develops a serious infection.

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Infections, predominantly of the upper respiratory tract, in some instances serious, have been reported with ILARIS. Generally, the observed infections responded to standard therapy. Isolated cases of unusual or opportunistic infections were reported during ILARIS treatment. In clinical trials, ILARIS has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Co-administration of ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections [*see Drug Interactions (7.1)*].

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of new tuberculosis and reactivation of latent tuberculosis (TB). It is possible that use of IL-1 inhibitors such as ILARIS increases the risk of reactivation of tuberculosis or of opportunistic infections.

Prior to initiating immunomodulatory therapies, including ILARIS, patients should be evaluated for active and latent tuberculosis infection. Appropriate screening tests should be performed in all patients. ILARIS has not been studied in patients with a positive tuberculosis screen, and the safety of ILARIS in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated according to standard medical practice prior to therapy with ILARIS. All patients should be instructed to seek medical advice if signs, symptoms, or high risk exposure suggestive of tuberculosis (e.g. persistent cough, weight loss, subfebrile temperature) appear during or after ILARIS therapy.

Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ILARIS.

5.2 Immunosuppression

The impact of treatment with anti-interleukin-1 (IL-1) therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including ILARIS, may result in an increase in the risk of malignancies.

5.3 Hypersensitivity

Hypersensitivity reactions have been reported with ILARIS therapy. No anaphylactic reactions have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity. ILARIS should not be administered to any patients with known clinical hypersensitivity to ILARIS [*see Contraindications (4) and Adverse Reactions (6.3)*].

5.4 Immunizations

Live vaccines should not be given concurrently with ILARIS [*see Drug Interactions (7.2)*]. Since no data are available on either the efficacy or on the risks of secondary transmission of infection by live vaccines in patients receiving ILARIS, live vaccines should not be given concurrently with ILARIS. In addition, because ILARIS may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ILARIS. No data are available on the effectiveness of vaccinations with inactivated (killed) antigens in patients receiving ILARIS. [*see Drug Interactions (7.2)*].

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ILARIS, adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current recommended immunization schedules at the website of the Centers for Disease Control, http://www.cdc.gov/vaccines/recs/schedules/).

6 ADVERSE REACTIONS

The data described herein reflect exposure to ILARIS in 104 adult and pediatric CAPS patients, (including 20 FCAS, 72 MWS, 10 MWS/NOMID (Neonatal Onset Multisystem Inflammatory Disorder) overlap, 1 non-FCAS non-MWS, and 1 mis-diagnosed in placebo-controlled (35 patients) and uncontrolled trials. Sixty-two patients were exposed to ILARIS for at least 6 months, 56 for at least 1 year and 4 for at least 3 years. A total of 9 serious adverse reactions were reported for CAPS patients. Among these were vertigo (2 patients), infections (3 patients), including intra-abdominal abscess following appendectomy (1 patient). The most commonly reported adverse reactions associated with ILARIS treatment in the CAPS patients were nasopharyngitis, diarrhea, influenza, headache, and nausea. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment. One patient discontinued treatment due to potential infection.

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Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience

Approximately 833 subjects have been treated with ILARIS in blinded and open-label clinical trials in CAPS and other diseases, and healthy volunteers. A total of 15 patients reported serious adverse reactions during the clinical program.

Study 1 investigated the safety of ILARIS in an 8-week, open-label period (Part 1), followed by a 24-week, randomized withdrawal period (Part 2), followed by a 16-week, open-label period (Part 3). All patients were treated with ILARIS 150 mg subcutaneously or 2 mg/kg if body weight was greater than or equal to 15 kg and less than or equal to 40 kg (see Table 1).

Since all CAPS patients received ILARIS in Part 1, there are no controlled data on adverse events (AEs). Data in Table 1 are for all AEs for all CAPS patients receiving canakinumab. In study 1, no pattern was observed for any type or frequency of adverse events throughout the three study periods.

Table 1 Number (%) of Patients with AEs by Preferred Terms, in > 10% of Patients in Parts 1 to 3 of the Phase 3 Trial for CAPS Patients

Preferred Term	ILARIS N=35 n (%)
n % of Patients with Adverse Events	35 (100)
Nasopharyngitis	12 (34)
Diarrhea	7 (20)
Influenza	6 (17)
Rhinitis	6 (17)
Nausea	5 (14)
Headache	5 (14)
Bronchitis	4 (11)
Gastroenteritis	4 (11)
Pharyngitis	4 (11)
Weight increased	4 (11)
Musculoskeletal pain	4(11)
Vertigo	4(11)

6.2 Vertigo

Vertigo has been reported in 9 to 14% of patients in CAPS studies, exclusively in MWS patients, and reported as a serious adverse event in two cases. All events resolved with continued treatment with ILARIS.

6.3 Hypersensitivity

Hypersensitivity reactions have been reported with ILARIS therapy. No anaphylactic reactions have been reported. ILARIS should not be administered to any patients with known clinical hypersensitivity to ILARIS [*see Contraindications (4) and Warnings and Precautions (5.3)*].

6.4 Injection Site Reactions

In Study 1, subcutaneous injection site reactions were observed in 9% of patients in Part 1 with mild tolerability reactions; in Part 2, one patient each (7%) had a mild or a moderate tolerability reaction and, in Part 3, one patient had a mild local tolerability reaction. No severe injection-site reactions were reported and none led to discontinuation of treatment.

6.5 Immunogenicity

A specific biosensor binding assay was used to detect antibodies directed against canakinumab in patients who received ILARIS. None of the 60 CAPS patients who had received ILARIS tested positive for treatment-emergent binding antibodies at the time points tested. Thirty-one of 60 CAPS patients had a duration of exposure to canakinumab >48

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weeks. The data obtained in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, underlying disease, and the number of patients tested. For these reasons, comparison of the incidence of antibodies to canakinumab with the incidence of antibodies to other products may be misleading.

6.6 Laboratory Findings

Hematology

During clinical trials with ILARIS, mean values decreased for white blood cells, neutrophils and platelets.

Hepatic transaminases

Elevations of transaminases have been observed in patients treated with ILARIS.

Bilirubin

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

7 DRUG INTERACTIONS

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

7.1 TNF-Blocker and IL-1 Blocking Agent

An increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors in another patient population. Use of ILARIS with TNF inhibitors may also result in similar toxicities and is not recommended because this may increase the risk of serious infections [*see Warnings and Precautions (5.1)*].

The concomitant administration of ILARIS with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacological interactions between ILARIS and a recombinant IL-1ra, concomitant administration of ILARIS and other agents that block IL-1 or its receptors is not recommended.

7.2 Immunization

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving ILARIS. Therefore, live vaccines should not be given concurrently with ILARIS. It is recommended that, if possible, pediatric and adult patients should complete all immunizations in accordance with current immunization guidelines prior to initiating ILARIS therapy [*see Warnings and Precautions (5.4)*].

7.3 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Canakinumab has been shown to produce delays in fetal skeletal development when evaluated in marmoset monkeys using doses 23-fold the maximum recommended human dose (MRHD) and greater (based on a plasma area under the time-concentration curve [AUC] comparison). Doses producing exposures within the clinical exposure range at the MRHD were not evaluated. Similar delays in fetal skeletal development were observed in mice administered a murine analog of canakinumab. There are no adequate and well-controlled studies of ILARIS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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Embryofetal developmental toxicity studies were performed in marmoset monkeys and mice. Pregnant marmoset monkeys were administered canakinumab subcutaneously twice weekly at doses of 15, 50 or 150 mg/kg (representing 23 to 230-fold the human dose based on a plasma AUC comparison at the MRHD) from gestation days 25 to 109 which revealed no evidence of embryotoxicity or fetal malformations. There were increases in the incidence of incomplete ossification of the terminal caudal vertebra and misaligned and/or bipartite vertebra in fetuses at all dose levels when compared to concurrent controls suggestive of delay in skeletal development in the marmoset. Since canakinumab does not cross-react with mouse or rat IL-1, pregnant mice were subcutaneously administered a murine analog of canakinumab 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 in a dose-dependent manner at all dose levels tested.

8.3 Nursing Mothers

It is not known whether canakinumab is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILARIS is administered to a nursing woman.

8.4 Pediatric Use

The CAPS trials with ILARIS included a total of 23 pediatric patients with an age range from 4 years to 17 years (11 adolescents were treated subcutaneously with 150 mg , and 12 children were treated with 2 mg/kg based on body weight greater than or equal to 15 kg and less than or equal to 40 kg). The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., Serum Amyloid A and C-Reactive Protein). Overall, the efficacy and safety of ILARIS in pediatric and adult patients were comparable. Infections of the upper respiratory tract were the most frequently reported infection. The safety and effectiveness of ILARIS in patients under 4 years of age has not been established [*see Pharmacokinetics (12.3)*].

8.5 Geriatric Use

Clinical studies of ILARIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported. In the case of overdose, it is recommended that the subject be monitored for any signs and symptoms of adverse reactions or effects, and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at asparagine 298 (Asn 298).

The biological activity of canakinumab is measured by comparing its inhibition of IL-1β-dependent expression of the reporter gene luciferase to that of a canakinumab internal reference standard, using a stably transfected cell line.

ILARIS is supplied in a sterile, single-use, colorless, 6 mL glass vial with coated stopper and aluminum flip-off cap. Each vial contains 180 mg of canakinumab as a white, preservative-free, lyophilized powder. Reconstitution with 1 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted canakinumab is a 150 mg/mL solution essentially free of particulates, clear to slightly opalescent, and is colorless or may have a slightly brownish-yellow tint. A volume of up to 1 mL can be withdrawn for delivery of 150 mg/mL canakinumab for subcutaneous administration. Each reconstituted vial contains 180 mg canakinumab, sucrose, L-histidine, L-histidine HCL monohydrate, polysorbate 80 and Sterile Water for Injection. No preservatives are present.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [CIAS1]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

The NLRP-3 gene encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation.

Canakinumab is a human monoclonal anti-human IL-1β antibody of the IgG1/κ isotype. Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1ra).

12.2 Pharmacodynamics

C-reactive protein and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Following ILARIS treatment, CRP and SAA levels normalize within 8 days.

12.3 Pharmacokinetics

Absorption

The peak serum canakinumab concentration (Cmax) of 16 ± 3.5 μg/mL occurred approximately 7 days after subcutaneous administration of a single, 150-mg dose subcutaneously to adult CAPS patients. The mean terminal half-life was 26 days. The absolute bioavailability of subcutaneous canakinumab was estimated to be 70%. Exposure parameters (such as AUC and Cmax) increased in proportion to dose over the dose range of 0.30 to 10 mg/kg given as intravenous infusion or from 150 to 300 mg as subcutaneous injection.

Distribution

Canakinumab binds to serum IL-1β. Canakinumab volume of distribution (Vss) varied according to body weight and was estimated to be 6.01 liters in a typical CAPS patient weighing 70 kg. The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous dosing of 150 mg ILARIS every 8 weeks.

Elimination

Clearance (CL) of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a typical CAPS patient weighing 70 kg. 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.

Pediatrics

Peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of ILARIS 150 mg or 2 mg/kg in pediatric patients. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab.

The mutagenic potential of canakinumab was not evaluated.

As canakinumab does not cross-react with rodent IL-1β, male and female fertility was evaluated in a mouse model using a murine analog of canakinumab. Male mice were treated weekly beginning 4 weeks prior to mating and continuing through 3 weeks after mating. Female mice were treated weekly for 2 weeks prior to mating through gestation day 3 or 4. The

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murine analog of canakinumab did not alter either male or female fertility parameters at subcutaneous doses up to 150 mg/kg.

14 CLINICAL STUDIES

The efficacy and safety of ILARIS for the treatment of CAPS was demonstrated in Study 1, a 3-part trial in patients 9 to 74 years of age with the MWS phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received ILARIS 150 mg and patients weighing 15 to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received ILARIS. Patients who achieved a complete clinical response and did not relapse by Week 8 were randomized into Part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed Part 2 or experienced a disease flare entered Part 3, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part 1, a complete clinical response was observed in 71% of patients one week following initiation of treatment and in 97% of patients by Week 8 (see Figure 1 and Table 2). In the randomized withdrawal period, a total of 81% of the patients randomized to placebo flared as compared to none (0%) of the patients randomized to ILARIS. The 95% confidence interval for treatment difference in the proportion of flares was 53% to 96%. At the end of Part 2, all 15 patients treated with ILARIS had absent or minimal disease activity and skin disease (see Table 2).

In a second trial, patients 4 to 74 years of age with both MWS and FCAS phenotypes of CAPS were treated in an open-label manner. Treatment with ILARIS resulted in clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in a majority of patients within 1 week.

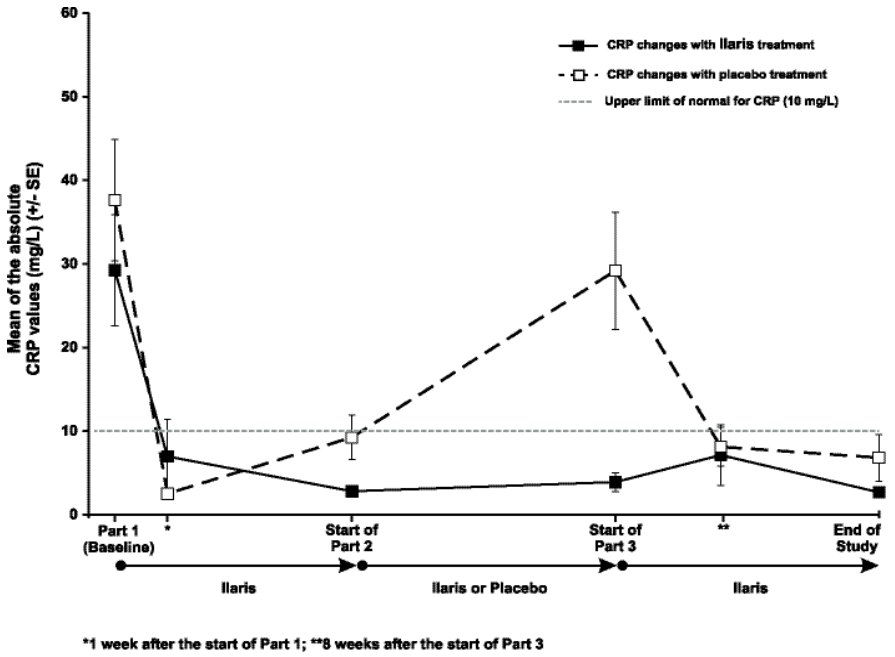
Table 2 Physician's Global Assessment of Auto-Inflammatory Disease Activity and Assessment of Skin Disease: Frequency Table and Treatment Comparison in Part 2 (Using LOCF, ITT Population)

		ILARIS N= 15		Placebo N= 16	
	Baseline	Start of Part 2 (Week 8)	End of Part 2	Start of Part 2 (Week 8)	End of Part 2
Absent	0/31 (0)	9/15 (60)	8/15 (53)	8/16 (50)	0/16 (0)
Minimal	1/31 (3)	4/15 (27)	7/15 (47)	8/16 (50)	4/16 (25)
Mild	7/31 (23)	2/15 (13)	0/15 (0)	0/16 (0)	8/16 (50)
Moderate	19/31 (61)	0/15 (0)	0/15 (0)	0/16 (0)	4/16 (25)
Severe	4/31 (13)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)
Absent	3/31 (10)	13/15 (87)	14/15 (93)	13/16 (81)	5/16 (31)
Minimal	6/31 (19)	2/15 (13)	1/15 (7)	3/16 (19)	3/16 (19)
Mild	9/31 (29)	0/15 (0)	0/15 (0)	0/16 (0)	5/16 (31)
Moderate	12/31 (39)	0/15 (0)	0/15 (0)	0/16 (0)	3/16 (19)
Severe	1/32 (3)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)

Markers of inflammation CRP and SAA normalized within 8 days of treatment in the majority of patients. Normal mean CRP (Figure 1) and SAA values were sustained throughout study 1 in patients continuously treated with canakinumab. After withdrawal of canakinumab in Part 2 CRP (figure 1) and SAA values again returned to abnormal values and subsequently normalized after reintroduction of canakinumab in Part 3. The pattern of normalization of CRP and SAA was similar.

Figure 1. Mean C-Reactive Protein Levels at the End of Parts 1, 2 and 3 of Study 1

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*1 week after the start of Part 1; **8 weeks after the start of Part 3

16 HOW SUPPLIED/STORAGE AND HANDLING

Carton of 1 vial…….NDC 0078-0582-61

Each 6 mL single-use vial of ILARIS contains a sterile, preservative free, white lyophilized powder containing 180 mg of canakinumab. Each vial is to be reconstituted with 1 mL of preservative-free Sterile Water for Injection in a 150 mg/mL solution.

Special Precautions for Storage

The unopened vial must be stored refrigerated at 2 to 8° C (36 to 46° F). Do not freeze. Store in the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ILARIS should be kept from light, and can be kept at room temperature if used within 60 minutes of reconstitution. Otherwise, it should be refrigerated at 2 to 8° C (36 to 46° F) and used within 4 hours of reconstitution. ILARIS does not contain preservatives. Unused portions of ILARIS should be discarded.

Keep this and all drugs out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling.

Patients should be provided the opportunity to read the Patient Information for ILARIS prior to the first treatment and any questions resulting from the patient's reading of the guide should be discussed.

17.1 Drug Administration

Healthcare providers should perform administration of ILARIS by the subcutaneous injection route.

17.2 Infections

Patients should be cautioned that ILARIS use has been associated with serious infections. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ILARIS. Treatment with ILARIS should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ILARIS, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ILARIS with other IL-1 blocking agents, such as rilonacept and anakinra is not recommended. Patients should be cautioned not to receive ILARIS if they have a chronic or active infection, including HIV, Hepatitis B or Hepatitis C.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

17.3 Vaccinations

Prior to initiation of therapy with ILARIS, physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ILARIS.

17.4 Injection-site Reactions

Physicians should explain to patients that a very small number of patients in the clinical trials experienced a reaction at the subcutaneous injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Healthcare providers should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

17.5 Hypersensitivity

Patients should be counseled to contact their healthcare provider immediately if they develop signs of allergic reaction such as difficulty breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations or low blood pressure.

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Information for Patients

See patient information leaflet.

Patient Information

ILARIS® (i-LAHR-us)

(canakinumab)

Read the Patient Information that comes with ILARIS before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is ILARIS? ILARIS is a prescription medicine injected just below the skin (subcutaneous) used in adults and children 4 years and older to treat auto-inflammatory diseases known as Cryopyrin-Associated Periodic Syndromes (CAPS), including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS),

It is not known if ILARIS is safe or effective in children under 4 years of age.

Who should not take ILARIS?

Do not take ILARIS if you:

- are allergic to canakinumab or any of the ingredients in ILARIS. See the end of this Patient Information leaflet for a complete list of the ingredients in ILARIS.

What should I tell my healthcare provider before taking ILARIS?

Before you take ILARIS, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have a history of infections that keep coming back
- have or have had HIV, Hepatitis B, or Hepatitis C
- have an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has or has had tuberculosis
- are scheduled to receive any immunizations (vaccines). You should not get ‘live vaccines’ if you take ILARIS.
- are pregnant or planning to become pregnant. It is not known if ILARIS will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking ILARIS.
- are breastfeeding or planning to breastfeed. It is not known if ILARIS passes into your breast milk. You and your healthcare provider should decide if you will take ILARIS or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you take:

- Medicines that affect your immune system
- IL-1 blocking agents such as Kineret® (anakinra), Arcalyst® (rilonacept)
- Tumor Necrosis Factor (TNF) inhibitors such as Enbrel® (etanercept)
- Humira® (adalimumab), or Remicade® (infliximab)
- Medicines that can affect enzyme metabolism. Ask your healthcare provider if you are not sure.

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Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ILARIS?

- Do not receive ILARIS if you have an infection.
- ILARIS is given by your healthcare provider every 8 weeks
- Your healthcare provider may change your dose if needed.

What are the possible side effects of ILARIS?

ILARIS can cause serious side effects including:

- serious infections. Symptoms of an infection may include:
    - a fever lasting longer than 3 days
    - a cough that does not go away
    - redness in one part of your body
    - warm feeling or swelling of your skin
- decrease your body's ability to fight infections (immunosuppression)

Other serious side effects may occur while you are taking and after you finish taking ILARIS including allergic reactions. Symptoms of an allergic reaction may include:

- rash (hives)
- swollen face
- problems breathing or swallowing

Call your healthcare provider right away or get emergency medical help if you have any of the signs of an infection or allergic reaction.

The most common side effects include:

- cold symptoms
- diarrhea
- flu (influenza)
- runny nose
- nausea
- headache
- injection site reaction (such as redness, swelling, warmth, itching)
- feeling like you are spinning (vertigo)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ILARIS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ILARIS

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use ILARIS for a condition for which it was not prescribed.

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This leaflet summarizes the most important information about ILARIS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ILARIS that was written for health professionals. For more information about ILARIS, call 1-877-452-7471 or visit www.ILARIS.com.

What are the ingredients in ILARIS?

Active ingredients: canakinumab

Inactive ingredients: sucrose, L-histidine, L-histidine HCl monohydrate, polysorbate 80, preservative-free Sterile Water for Injection.

What is CAPS Disease?

In patients with CAPS, the body produces excessive amounts of a chemical messenger called interleukin-1 beta (IL-1β). This may lead to symptoms such as fever, headache, fatigue, skin rash, painful joints and muscles. In some patients, more severe outcomes such as hearing impairment are observed.

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