ACZ885, CANAKINUMAB, ILARIS®

Managed Access Program (MAP) to provide access to canakinumab treatment of cytokine release syndrome (CRS) in patients with COVID-19-induced pneumonia

Guidance and information package

This guidance will be sent to each Treating Physician upon approval to his/her independent request for canakinumab. It should be used as a guidance document for the treatment and monitoring of patients on MAP to ensure adherence to the Novartis safety standards. This Guidance shall be provided along with the ***GENERAL CONDITIONS FOR THE SUPPLY OF PRODUCT in the context of COVID 19.***

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1 Treatment guidance

The purpose of this document is to provide the Treating Physician with all available product information to administer canakinumab for cytokine release syndrome (CRS) to eligible patients with COVID-19-induced pneumonia. The patient's Treating Physician must comply with all local health authority regulations before moving forward with a request for a Novartis drug.

Please refer to the latest Investigator's Brochure (IB) and/or approved product information for overview of drug including non-clinical and clinical experience, risk and benefits, including the following:

- **Currently there is no clinical experience with canakinumab in the treatment of cytokine release syndrome (CRS) nor in patients with COVID-19-induced pneumonia**
    - However, canakinumab could be used in CRS given the cytokine profiling of patients with severe COVID-19 which is associated with elevated levels of interleukin (IL)-1, IL-2, IL-7, IL-6, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumor necrosis factor-α [Mehta et al 2020; Zhou et al 2020].
- **The terminal half-life of canakinumab ranges from 22.9 to 25.7 days (therefore, complete elimination of canakinumab would occur 60 to 100 days after administration).**
- **Serious Infections Warning: Canakinumab is associated with an increased incidence of serious infections. Therefore, patients should be monitored carefully for signs and symptoms of infections during and after treatment with canakinumab.**
- **Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to severe infections.**

Novartis will continue to provide any new safety information to the Treating Physicians as they emerge. Careful benefit/risk evaluation should be conducted when considering the use of canakinumab for unapproved indications, and the access to canakinumab will be provided unless experience in COVID-19 patients reveals a lack of efficacy or an unacceptable safety risk.

2 Program closure / patient transition specifications

This program will provide access to canakinumab for eligible patients until:

- Alternative treatment options are available and/or
- A change in the overall benefit/risk profile of canakinumab in this patient population

3 Patient eligibility

3.1 Managed Access-specific criteria

The following criteria must be fulfilled for the provision of managed access to canakinumab:

- An independent unsolicited request should be received from the Treating Physician, Health Authorities, Institutions or Governments;
- The patient to be treated has a COVID-19-related serious or life-threatening disease or condition and there is no comparable or satisfactory alternative treatment available to this patient;
- The patient is not eligible or able to enroll in a clinical trial;
- There is a potential patient benefit to justify the potential risk of the treatment use, and the potential risk is not unreasonable in the context of the disease or condition to be treated;
- Novartis has adequate supply of the product and providing the product will not interfere with ongoing clinical trial(s) or overall development program;
- Such access provision as described above is allowed as per local laws and regulations.

3.2 Inclusion criteria

- Age ≥ 18 years old;
- Clinical diagnosis of SARS-CoV-2 virus by PCR, or by other approved diagnostic methodology, or, with presumptive diagnosis of COVID-19 (other respiratory causes ruled out and COVID-19 test pending);
- Hospitalized with COVID-19-induced pneumonia;
- Elevated CRP or ferritin levels;
- Body weight ≥ 40kg.

3.3 Exclusion criteria

- Eligible patients must not have a history of hypersensitivity to any drugs or metabolites of similar chemical classes as canakinumab;
- On the day of canakinumab treatment initiation; treatment with biologic immunomodulators or immunosuppressant drugs, including but not limited to TNF inhibitors and anti-IL-17 agents. Immunomodulators (topical or inhaled) for asthma and atopic dermatitis are permitted as are systemic low-dose corticosteroids (e.g. ≤10 mg prednisone per day);
- Use of tocilizumab within 3 weeks prior to dosing with canakinumab;
- Suspected or known active bacterial, fungal, or parasitic infection (besides COVID-19);
- Patients with significant neutropenia (ANC <1000/mm^3);
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) prior to canakinumab dose.

4 Dosing information

Currently there is no clinical experience with canakinumab in the treatment of cytokine release syndrome (CRS) in patients with COVID-19-induced pneumonia, which is not an approved indication.

The proposed canakinumab dose is 600 mg in 250 mL of 5% dextrose infused intravenously (i.v.) over 2 hours (for patients between 40-60 kg see Table below).

The dose should not exceed approximately 10 mg/kg.

Canakinumab dose by body weight

Canakinumab in 250 mL of 5% dextrose		
Body weight	Dose of canakinumab	Volume from Vial (150 mg/mL)
> 60 kg	600 mg	4.0 mL
40 to 60 kg	450 mg	3.0 mL

4.1 Rationale for the proposed dose and route of administration

The i.v. delivery of a high canakinumab dose, which is supported by available safety data (see below), ensures a fast decrease in pharmacologically active IL-1β and is expected to reduce IL-1 β signaling to marginal levels within hours.

The maximal total dose proposed therefore is 750 mg i.v., equating to 10 mg/kg i.v. in a 75 kg patient. A body weight normalization was not considered useful, since it adds complexity. In higher weight adult patients the canakinumab dose is typically not adjusted to body weight since the clearance of antibodies is increasing less then linear with body weight.

The doses of 10 mg/kg or 600 mg i.v. canakinumab have been previously investigated in 288 patients or healthy volunteers (including children >3 years of age) as single or repeated doses in autoinflammatory conditions, gouty arthritis, asthma, type 2 diabetes mellitus, and ocular conditions in the development program. Canakinumab was safe and well tolerated in all studies, with no safety concern identified by analysis of AE, laboratory or vital signs. [IB version 18 Aug 2019].

4.2 Dosing in currently approved indications

Currently approved dosing regimens (either in the US or EU) for canakinumab administered subcutaneously include the following:

1. For Still's disease, the dose in adults, adolescents and children ≥ 2 years of age with body weight ≥7.5 kg is 4 mg/kg (up to maximum of 300 mg).

2. For cryopyrin-associated periodic syndromes (CAPS), the dose in adults, adolescents and children ≥ 4 years of age is
   - 150 mg for patients with body weight > 40 kg (up to 600 mg in some indications)
   - 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
   - 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg

   For children 2 to < 4 years of age, 4 mg/kg for patients with body weight ≥ 7.5 kg

Recommended duration of treatment is dependent on the indication, and is typically repeated every 4 weeks, if clinically needed, in approved indications. Please see IB or approved product of information.

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

4.3 Concomitant medications

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

4.3.1 Permitted concomitant therapy requiring caution and/or action (if applicable)

No formal drug-drug interaction studies have been conducted with canakinumab.

Elimination pathways for IgG type monoclonal antibodies such as canakinumab are distinct from metabolic pathways of small molecules. The IgG-based molecules are cleared from the body by a combination of processes such as proteolysis by the liver, elimination by the reticular endothelium system (RES) and nonspecific endocytosis, whereas small molecular weight drugs are typically eliminated through CYP450-mediated oxidation pathways and are therefore not expected to affect the pharmacokinetics of canakinumab.

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

Please refer to the IB or approved product information.

4.3.2 Prohibited concomitant therapy

See above for potential drug-drug interactions. Please refer to the IB or approved product information.

4.4 Patient discontinuation

The patient may voluntarily withdraw from treatment for any reason, at any time.

The Treating Physician should discontinue treatment for the patient and/or withdraw the patient from treatment if, on balance, he/she believes that continuation would be detrimental to the patient’s well-being.

The patient may continue treatment until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the Treating Physician or withdrawal of consent.

5 Product supply

Product must be received by designated personnel at the treating site, handled and stored safely and properly, and kept in a secured location to which only the Treating Physician and designated site personnel have access. Upon receipt, product should be stored according to the instructions specified in the IB or approved product information.

5.1 Disposal and destruction

Destruction of product should follow local laws/regulation. The leftover medication may be directly destroyed at the site or be sent to a local 3rd party within the country with the proper qualifications to perform this task.

6 Recommended patient monitoring parameters / assessments prior to canakinumab treatment initiation

- Physical Examination with vital signs, height and weight.
- Chest x-ray and oxygen saturation.
- Electrocardiogram (ECG): a standard 12 lead ECG with QTc Interval report.
- Pregnancy Test (recommended for females of child-bearing age): Before initiation of canakinumab, a serum pregnancy test should be performed.
- Hematology including hemoglobin, hematocrit, total WBC count with differential, and platelet count.
- Chemistries including urea or BUN, creatinine, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), calcium, lipase, amylase, potassium, magnesium, and phosphorus.
- Concomitant Medications: please see section 4.3.
- Adverse events should be monitored continuously from the time of consent; see section 9.

6.1 Patient medical and medication history

Relevant medical history on each patient should be provided to Novartis prior to initiation of canakinumab.

Assessment of latent infections (including Cytomegalovirus, Epstein-Barr Virus, Human Herpes Virus-6, Hepatitis B Virus, Hepatitis C Virus, and tuberculosis) should be made and if present, patients should be monitored closely for reactivation.

It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as canakinumab increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be

evaluated for both active and latent tuberculosis infection. See IB or approved product information.

6.2 Safety and tolerability assessments

For women of child-bearing potential serum pregnancy test is recommended before initiation of canakinumab.

The following tests should be conducted prior to canakinumab initiation

- Vital signs
- Hematology (CBC)
- Chemistries including liver and renal function tests
- 12-lead ECG

7 Data collection

7.1 Rationale for data collection

The primary purpose of a MAP is to provide access to medication and not to collect data. However, some minimal information will be obtained to allow the sponsor to approve admission of a patient to the MAP (see Section 2) and to assure the sponsor on continued patient benefit.

Except for standard safety reporting, data collection may be waived if not allowed or not recommended by local laws, regulations, or guidance.

7.2 Type of data to be collected

Data of the following categories will be collected:

- Patient demographics
- Disease characteristics at baseline
- Baseline concomitant medication
- Canakinumab treatment dose
- Follow up information on each patient 14 days post initiation of treatment

Standard safety reporting will performed as per Section 8 and information on patient benefit will be collected on a follow up which will be sent to the Treating Physician 14 days after the approval of the request.

No additional information will be collected unless required by local regulations.

8 Safety reporting requirements

Reporting safety information to the local Health Authority and/or to EC/IRB must follow local regulatory requirements. Reporting of safety information to Novartis must follow the provisions of the GENERAL CONDITIONS FOR THE SUPPLY OF PRODUCT in the context of COVID 19, using the Novartis Adverse Event forms for Managed Access and sent to the respective Novartis Local Patient Safety Department. Details on reporting of safety information are described in section 8.1.

8.1 Adverse event reporting

The Treating Physician acknowledges that it is his/her responsibility to report to Novartis Local Patient Safety Department any relevant information about the safety of the Product, including, but not limited to (a) any Serious Adverse Events (SAEs), and (b) any additional safety reports submitted to the local Health Authority and Ethics Committee / IRB according to the applicable local laws and regulations.

9 Patient informed consent

The patient informed consent must be obtained in accordance with local regulatory requirements and institutional policy and is the responsibility of the treating physician.

10 References

Mehta et al 2020; COVID-19: consider cytokine storm syndromes and immunosuppression. thelancet.com Published online March 13, 2020 https://doi.org/10.1016/S0140-6736(20)30628-0

Zhou F, Yu T, Du R, Fan G, Liu Y, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Thelancet.com Published Online March 9, 2020 https://doi.org/10.1016/S0140-6736(20)30566-3]