FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR KINERET

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use KINERET® under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for KINERET®.

KINERET® (anakinra) injection, for subcutaneous use
Original EUA Authorized Date: 11/2022

----------EUA FOR KINERET----------
The U.S. Food and Drug Administration has issued an EUA for the emergency use of KINERET for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

However, KINERET is not approved for this use.

See Section 1.1 for criteria to identify patients who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma suPAR.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of KINERET in adults with COVID-19 is 100 mg administered daily by subcutaneous injection for 10 days. (2.1)
- In COVID-19 patients who have severe renal insufficiency or end stage renal disease (creatinine clearance < 30 mL/min, estimated from serum creatinine levels) consider a dose of 100 mg of KINERET administered every other day for 5 total doses over 10 days. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 mg/0.67 mL solution in a single-use prefilled syringe for subcutaneous injection. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to E coli-derived proteins, anakinra, or to any component of the product. (4)

----------WARNINGS AND PRECAUTIONS----------
- KINERET has been associated with an increase of serious infections in patients with rheumatoid arthritis. (5.1)
- KINERET is not recommended for use in combination with Tumor Necrosis Factor (TNF) blocking agents. (5.2)
- Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported. (5.3)
- The impact of treatment with KINERET on the development of malignancies is not known. (5.4)
- Avoid live vaccines during treatment with KINERET. (5.5)
- Neutropenia can occur with treatment with KINERET. Assess neutrophil counts prior to initiating KINERET treatment. COVID-19 patients with < 1500 neutrophils/mm^3 were excluded from study participation. (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 1%) are transaminases increased, neutropenia, rash, and injection site reactions. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to KINERET (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Swedish Orphan Biovitrum at email medinfo.us@sobi.com or call 1-866-773-5274 (6.2).

----------DRUG INTERACTIONS----------
KINERET is not recommended for use in combination with TNF blocking agents. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment: This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. (8.6)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of KINERET for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR) *[see Section (1.1)]*.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition.
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that:
    - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s).
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

Veklury (remdesivir), a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure. Veklury has demonstrated antiviral activity against SARS-CoV-2; whereas KINERET is an IL-1 receptor antagonist that blocks the IL-1 signaling pathway, which is involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19, offering a different mechanism of action.

Olumiant (baricitinib), a Janus kinase (JAK) inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen and non-invasive ventilation. KINERET offers an alternative mechanism of action as an IL-1 receptor antagonist. IL-1 is another component of the complex hyperinflammatory response thought to contribute to worsening of COVID-19. In addition, KINERET has a subcutaneous route of administration, whereas, Olumiant is available as tablets; thus KINERET is offering an alternative route of administration to some patients who are hospitalized (e.g. for patients who are unable to swallow tablets).

Other therapeutics are currently authorized for the same use as KINERET. For additional information on all products authorized for the treatment of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policyframework/emergency-use-authorization.

For information on clinical studies of KINERET and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

1.1 Patient Population Identification

KINERET is authorized for emergency use for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma suPAR.

In the SAVE-MORE trial used to support the efficacy and safety of KINERET in COVID-19, key exclusion criteria were: pO2/FiO2 ratio < 150 mmHg, requirement for non-invasive ventilation (NIV), requirement for mechanical ventilation (MV), requirement for extra-corporeal membrane oxygenation (ECMO), and < 1500 neutrophils/mm^3.

All enrolled patients were required to have a plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥ 6 ng/mL *[see Clinical Studies (14.1)]*. The suPAR assay is not commercially available in the United States. In order to identify a comparable population as was studied in the SAVE-MORE trial, an alternative patient identification method was developed to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics. Patients meeting at least three of the following eight criteria are considered likely to have suPAR ≥ 6 ng/mL at baseline:

1. Age ≥ 75 years
2. Severe pneumonia by WHO criteria[1]
3. Current/previous smoking status
4. Sequential Organ Failure Assessment (SOFA)[2] score ≥ 3
5. Neutrophil-to-lymphocyte ratio (NLR) ≥ 7
6. Hemoglobin ≤ 10.5 g/dL
7. Medical history of ischemic stroke
8. Blood urea ≥ 50 mg/dL and/or medical history of renal disease

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for COVID-19

The recommended dosage of KINERET for the treatment of adults with COVID-19 is 100 mg administered daily by subcutaneous injection for 10 days.

Each syringe is intended for a single use. A new syringe must be used for each dose. Any unused portion after each dose should be discarded.

2.2 Renal Impairment

Consider administration of KINERET 100 mg every other day by subcutaneous injection for a total of 5 doses over 10 days in patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Important Administration Instructions

The prescribed dose of KINERET should be administered according to the instructions for use and any unused portions discarded. After administration of KINERET it is essential to follow the proper procedure for disposal of syringes and any residual drug. See the “Instructions for Use” in the FDA-approved Prescribing Information for detailed instructions on the handling and injection of KINERET.

Do not use KINERET beyond the expiration date shown on the carton. Visually inspect the solution for particulate matter and discoloration before administration. There may be trace amounts of small, translucent-to-white amorphous particles of protein in the solution. The prefilled syringe should not be used if the solution is discolored or cloudy, or if foreign particulate matter is present. If the number of translucent-to-white amorphous particles in a given syringe appears excessive, do not use this syringe.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/0.67 mL solution in a single-use prefilled syringe for subcutaneous injection.

4 CONTRAINDICATIONS

KINERET is contraindicated in patients with known hypersensitivity to *E. coli* derived proteins, KINERET, or any components of the product *[see Warnings and Precautions (5.3)].*

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

KINERET has been associated with an increased incidence of serious infections (2%) vs. placebo (< 1%) in clinical trials of patients with rheumatoid arthritis (RA). In a placebo-controlled study in COVID-19 patients, serious infections were observed in 9.1% of patients (37/405) treated with KINERET and 16.4% of patients (31/189) treated with placebo. In patients with COVID-19, monitor for signs and symptoms of new infections during and after treatment with KINERET. There is limited information regarding the use of KINERET in patients with COVID-19 and concomitant active serious infections. The risks and benefits of treatment with KINERET in COVID-19 patients with other concurrent infections should be considered.

The safety and efficacy of KINERET in immunosuppressed patients or in patients with chronic infections have not been evaluated.

5.2 Use with TNF blocking Agents

An increased rate of serious infections was observed in patients with RA who received KINERET and etanercept concurrently (7%) compared with etanercept alone (0%). KINERET is not recommended for use in combination with TNF blocking agents.

The combination of KINERET with TNF blocking agents and other anti-cytokine treatments has not been evaluated in COVID-19 patients.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported with KINERET. If a severe hypersensitivity reaction occurs, administration of KINERET should be discontinued and appropriate therapy initiated.

5.4 Immunosuppression

The impact of treatment with KINERET on the development of malignancies in COVID-19 patients is not known.

5.5 Immunizations

In a placebo-controlled clinical trial (n = 126), no difference was detected in anti-tetanus antibody response between the KINERET and placebo treatment groups when the tetanus/diphtheria toxoids vaccine was administered concurrently with KINERET. No data are available on the effects of vaccination with other inactivated antigens, or COVID-19 vaccines, in patients receiving KINERET. No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving KINERET. Therefore, avoid live vaccines during treatment with KINERET.

5.6 Neutropenia

Patients receiving KINERET may experience a decrease in neutrophil counts. There is limited information on the effect of KINERET on the neutrophil count of patients with COVID-19. COVID-19 patients with < 1500 neutrophils/mm3 were excluded from participation in the SAVE and SAVE-MORE studies. Therefore, assess neutrophil counts prior to initiating KINERET treatment for COVID-19 and monitor for neutropenia according to current clinical practices *[see Adverse Reactions (6.1)].*

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of KINERET in COVID-19 that supported EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of KINERET for RA, Neonatal-Onset Multisystem Inflammatory Disease (NOMID), Deficiency of Interleukin-1 Receptor Antagonist (DIRA), and may not reflect the rates observed in clinical practice.

The safety data described in this section are based on a randomized placebo-controlled study of 405 Kineret-treated patients hospitalized with COVID-19 pneumonia (SAVE-MORE study). During the study, there were 18 (4.4%) deaths in the KINERET arm and 17 (9.0%) in the placebo arm. Serious infections occurred in 37 patients (9.1%) in the KINERET arm and in 31 patients (16.4%) in the placebo arm. The adverse events reported more frequently in patients receiving Kineret compared to placebo, at a frequency of at least 1% are described in Table 1.

The overall safety profile in patients with COVID-19 treated with Kineret is similar to that in Kineret-treated patients with the approved indication RA.

Table 1. Adverse Events Occurring in at Least 1% of Patients in the KINERET Arm and at least 1% More Frequently than Observed in the Placebo Arm Through Day 90

Adverse Reactions	SoC + PLACEBO (N=189[a] n (%)	SoC + KINERET (N=405) [a] n (%)
Transaminases increased	52 (27.5)	125 (30.8)
Gamma-glutamyltransferase increased	22 (11.7)	56 (13.8)
Leukopenia	2 (1.1)	14 (3.5)
Neutropenia	1(0.5)	12 (3.0)
Rash	3 (1.5)	15 (3.7)
Hypernatremia	15 (7.9)	39 (9.6)
Constipation	14 (7.4)	37 (9.1)
Hyperkalemia	14 (7.4)	37 (9.1)
Anxiety	12 (6.3)	33 (8.1)
Hypothermia	8 (4.2)	30 (7.4)
Acute Kidney Injury	10 (5.2)	26 (6.3)

[a]Patients are counted once for each category regardless of the number of events

6.2 Adverse Reactions from Spontaneous Reports

Refer to Section 6 Adverse Reactions of the FDA-approved Prescribing Information for additional information on adverse reactions associated with chronic use of KINERET.

6.3 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to KINERET within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)

- A statement “KINERET use for COVID-19 under Emergency Use Authorization (EUA)” under the “**Describe Event, Problem, or Product Use/Medication Error”** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient’s preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Sobi Inc
Email: medinfo.us@sobi.com or call at 1-866-773-5274

The prescribing health care provider and/or the provider’s designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of KINERET.

*Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial distruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

7 DRUG INTERACTIONS

No drug-drug interaction studies in human subjects have been conducted. Toxicologic and toxicokinetic studies in rats did not demonstrate any alterations in the clearance or toxicologic profile of either methotrexate or KINERET when the two agents were administered together.

7.1 TNF Blocking Agents

A higher rate of serious infections has been observed in patients treated with concurrent KINERET and etanercept therapy than in patients treated with etanercept alone *[see Warnings and Precautions (5.2)]*. Two percent of patients treated concurrently with KINERET and etanercept developed neutropenia (ANC < 1 x 10^9/L). Use of KINERET in combination with TNF blocking agents is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from retrospective studies and case reports on KINERET use in pregnant women are insufficient to identify a drug associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. In animal reproduction studies, subcutaneous administration of anakinra to pregnant rats and rabbits during organogenesis demonstrated no evidence of fetal harm at doses up to 25 times the maximum recommended human dose (MRHD).The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The available data from retrospective studies and case reports of anakinra-exposed pregnancies have not identified an increased frequency or pattern of birth defects, miscarriage, or adverse maternal or fetal outcomes. An international multi-center retrospective study of pregnancy outcomes with interleukin-1 inhibitors reported on 23 anakinra-exposed pregnancies. There were 21 live births of healthy infants, 1 miscarriage, and 1 infant with left renal agenesis. The estimated background rate of detected renal malformations is 0.2-2% of all newborns. Overall, these data cannot definitively establish or exclude any anakinra-associated risks during pregnancy. Methodological limitations of these data include small sample size and the inability to control for confounders such as the timing of drug exposure, underlying maternal disease, and concomitant medication use.

Animal Data

Animal reproduction studies were conducted in rats and rabbits. In embryo-fetal development studies, anakinra was administered throughout the period of organogenesis at the subcutaneous doses of 12.5, 50, and 200 mg/kg/day to pregnant rats from gestation days (GD) 7 to 17 and pregnant rabbits from GD 6 to 18. In these studies, anakinra at doses up to 25 times the MRHD (on a mg/kg basis at maternal subcutaneous doses up to 200 mg/kg/day) revealed no evidence of harm to the fetus.

8.2 Lactation

Risk Summary

There are no data on the presence of anakinra in either human or animal milk or the effects on milk production. Available published data from a small retrospective study and postmarketing case reports do not establish an association between maternal anakinra use during lactation and adverse effects on breastfed infants. The limited clinical data during lactation precludes a clear determination of the risk of KINERET to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for KINERET and any potential adverse effects on the breastfed infant from KINERET or from the underlying maternal condition.

8.4 Pediatric Use

The emergency use of KINERET is not authorized or approved for the treatment of coronavirus disease 2019 (COVID-19) for pediatric patients less than 18 years of age.

8.5 Geriatric Use
In a placebo-controlled study in COVID-19 patients, 250/594 (42%) were 65 years of age or older (KINERET 172/405, placebo 78/189). No differences in safety or effectiveness were observed between these patients and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

8.6 Renal Impairment
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function *[see Clinical Pharmacology (12.3)].*

KINERET has not been studied in COVID-19 patients with end-stage renal failure necessitating hemofiltration or peritoneal hemodialysis.

8.7 Hepatic Impairment
No formal studies have been conducted examining the pharmacokinetics of KINERET administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE
In sepsis trials no serious toxicities attributed to KINERET were seen when administered at mean calculated doses of up to 35 times those given patients with COVID-19 over a 72-hour treatment period.

11 DESCRIPTION
KINERET (anakinra) is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). KINERET differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. KINERET consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an *E coli* bacterial expression system.

KINERET is supplied in single use prefilled glass syringes with 29 gauge needles as a sterile, clear, colorless-to-white, preservative free solution for daily subcutaneous (SC) administration. The solution may contain trace amounts of small, translucent-to-white amorphous proteinaceous particles. Each prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing anhydrous citric acid (1.29 mg), disodium EDTA (0.12 mg), polysorbate 80 (0.70 mg), and sodium chloride (5.48 mg) in Water for Injection, USP.

The prefilled syringe contains an outer rigid plastic needle shield attached to an inner needle cover. The syringe or needle shield components are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
KINERET blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs.

Refer to **Section 12.1 Mechanism of Action** of the FDA-approved Prescribing Information for additional information on the mechanism of action in the approved indications for Kineret.

12.3 Pharmacokinetics
The pharmacokinetics of Kineret has not been studied in patients with COVID-19.
The absolute bioavailability of KINERET after a 70 mg subcutaneous bolus injection in healthy subjects (n = 11) is 95%.

In subjects withRA, maximum plasma concentrations of KINERET occurred 3 to 7 hours after subcutaneous administration of KINERET at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of KINERET was observed after daily subcutaneous doses for up to 24 weeks.

The influence of demographic covariates on the pharmacokinetics of KINERET was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily subcutaneous injection of KINERET at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated KINERET clearance increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance.

In Neonatal-Onset Multisystem Inflammatory Disease (NOMID) patients, at a median SC dose of 3 mg/kg once daily and a median treatment time of 3.5 years, the median (range) steady-state serum exposure of anakinra was C_{max} 3628 (655–8511) ng/mL (n=16) and C_{24h} 203 (53–1979) ng/mL (n=16). The median (range) half-life of anakinra was 5.7 (3.1–28.2) hours (n=12). There was no obvious gender difference.

Patients With Renal Impairment: The mean plasma clearance of KINERET in subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively. In severe renal insufficiency and end stage renal disease (creatinine clearance < 30 mL/min[1]), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of KINERET was removed by hemodialysis or continuous ambulatory peritoneal dialysis. Based on these observations, a dose schedule change should be considered for subjects with severe renal insufficiency or end stage renal disease *[see Dosage and Administration (2.2)].*

Patients with Hepatic Dysfunction: No formal studies have been conducted examining the pharmacokinetics of KINERET administered subcutaneously in patients with hepatic impairment**.**

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of KINERET were not conducted. KINERET had no effects on fertility and reproductive performance indices in male and female rats subcutaneous doses up to 200 mg/kg/day (approximately 25 times the MRHD on a mg/kg basis).

14 CLINICAL STUDIES

14.1 Clinical Study in COVID-19

SAVE-MORE (NCT04680949) was a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Kineret in adult (≥18 years) patients with COVID-19 pneumonia who were at risk of developing severe respiratory failure (SRF), defined as pO2/FiO2 < 150 mmHg necessitating high flow oxygenation (HFO)/NIV/MV. All patients were hospitalized adults with COVID-19 pneumonia, radiologically confirmed by chest X-ray or CT, but had not progressed to SRF. All enrolled patients in this study were required to have a plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥ 6 ng/mL. The suPAR assay is not commercially available for use in the United States, *[see Emergency Use Authorization (1.1)]*. Key exclusion criteria were pO2/FiO2 < 150 mmHg, requirement for NIV, requirement for MV, requirement for ECMO, and < 1500 neutrophils/mm^3. The mean age of participants was 61.9 years (standard deviation [SD] 12.1 years), and 57.9% were male.

Efficacy analyses at Day 28 were performed using all randomized patients who maintained consent for data usage comprising 594 patients of whom 189 patients were randomized to the placebo+Standard of Care (SoC) arm and 405 patients to the anakinra 100 mg daily+SoC arm for 10 days.

At the start of treatment, 91% of patients had severe COVID-19 pneumonia and required low- or high-flow supplementary oxygen, 9% of patients had moderate COVID-19 pneumonia. 86% of patients received dexamethasone.

The primary endpoint of the study was the 11-point WHO Clinical Progression ordinal Scale (CPS) which was compared between the two arms of treatment by Day 28. The 11-point WHO- CPS provides a measure of illness severity across a range from 0 (not infected); 1-3 (mild disease), 4-5 (hospitalized – moderate disease), 6-9 (hospitalized – severe disease with increasing degrees of NIV, MV and ECMO) to 10 (dead).

Patients treated with KINERET had lower odds of more severe disease according to the WHO-CPS at Day 28 compared to placebo (odds ratio: 0.37 [95% CI 0.26 to 0.50]).

By Day 28, there were 13 deaths (6.9%) in the placebo arm and 13 deaths (3.2%) in the KINERET arm (hazard ratio (HR): 0.48 [95% CI 0.22, 1.04]; risk difference: -3.7% [95% CI -7.7%, 0.3%]). By Day 60, there were 18 deaths (9.7%) in the placebo arm and 21 deaths (5.3%) in the KINERET arm (HR: 0.56 [95% CI 0.30, 1.04]; risk difference -4.4% [95% CI -9.2%, 0.4%]).

By Day 28, there were 62 (32.8%) patients in the placebo arm and 86 (21.2%) patients in the KINERET arm with SRF (HR: 0.66 [95% CI 0.48, 0.92]; risk difference -11.6% [95% CI -19.4%, -3.8%]).

The endpoints were not multiplicity controlled.

15 REFERENCES

1. World Health Organization . (2020, March 13). *Clinical management of severe acute respiratory infection (SARI) when covid-19 disease is suspected*. Interim Guidance . Retrieved October 13, 2022, from https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov

2. HHS Technical Resources, Assistance Center, and Information Exchange. (2020, December 21). *Sofa score: What it is and how to use it in triage - hhs.gov*. SOFA Score: What it is and How to Use it in Triage. Retrieved October 13, 2022, from https://files.asprtracie.hhs.gov/documents/aspr-tracie-sofa-score-fact-sheet.pdf

16 HOW SUPPLIED/STORAGE AND HANDLING

KINERET is supplied in single-use preservative free, prefilled glass syringes with 29 gauge needles. Each prefilled glass syringe contains 100 mg of anakinra per 0.67 mL. The full syringe contains 100 mg anakinra. KINERET is dispensed in a 1 x 7 syringe dispensing pack containing 7 syringes (NDC 66658-234-07).

Storage

Store KINERET in the refrigerator at 2°C to 8°C (36°F to 46°F). **DO NOT FREEZE OR SHAKE.** Protect from light.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the "FACT SHEET FOR PATIENTS AND CAREGIVERS" (**www.KineretRxHCP.com/EUA**) and provide them with a copy of this Fact Sheet prior to administration of KINERET. However, if providing this information will delay the administration of KINERET to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after KINERET administration

Manufactured by Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden

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