December 19, 2022

Emergency Use Authorization
Kineret® (anakinra) injection for the treatment of COVID-19 in certain hospitalized patients

Background & Current Status[1,2]:

On November 8, 2022, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for Kineret® (anakinra) injection 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 and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)**. Kineret® is currently FDA-approved for the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes and deficiency of IL-1 receptor antagonist.

Dosage and Administration[3]:

The recommended dosage of Kineret® for the treatment of adults with COVID-19 is 100mg administered daily by subcutaneous injection for 10 days. Consider administration of Kineret® 100mg 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 (creatinine clearance <30 mL/min).

Efficacy & Safety Data[2,3,5]:

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.

In the SAVE-MORE trial, key exclusion criteria used to support the efficacy and safety of Kineret in COVID-19 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/mm3.

All enrolled patients were required to have a plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥6 ng/mL. 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
3. Current/previous smoking status
4. Sequential Organ Failure Assessment (SOFA) 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

The primary endpoint of the study was the 11-point World Health Organization Clinical Progression ordinal Scale (WHO-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: 0.48, 95% CI: 0.22 to 1.04; Risk Difference: -3.7%, 95% CI: -7.7% to 0.3%). By Day 60, there were 18 deaths (9.7%) in the placebo arm and 21 deaths (5.3%) in the Kineret® arm (Hazard Ratio: 0.56, 95% CI: 0.30 to 1.04; Risk Difference: -4.4%, 95% CI: -9.2% to 0.4%).

By Day 28, there were 62 patients (32.8%) in the placebo arm and 86 patients (21.2%) in the Kineret® arm with severe renal failure (Hazard Ratio: 0.66, 95% CI: 0.48 to 0.92; Risk Difference -11.6%, 95% CI: -19.4% to -3.8%).

The most common adverse reactions (incidence ≥1%) with use of Kineret® are elevated liver enzymes, neutropenia, rash, and injection site reactions. Kineret® has been associated with an increase of serious infections in patients with rheumatoid arthritis. Kineret® is not recommended for use in combination with Tumor Necrosis Factor (TNF) blocking agents. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported. The impact of treatment with Kineret® on the development of malignancies is not known. Patients should avoid live vaccines during treatment with Kineret®. Neutropenia can occur with treatment with Kineret®.

Providers should assess neutrophil counts prior to initiating Kineret treatment®. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. Patients with known hypersensitivity to E. coli-derived proteins or any components of the product should not be given Kineret®.

Current EUA Fact Sheets[3,4]:

As a convenience, Fact Sheets for Kineret® are accessible below:

- Healthcare Providers
- Patients, Parents and Caregivers

Conditions of Authorization for Healthcare Facilities under the Emergency Use Authorization[2]:

- Ensure that healthcare facilities are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of Kineret.
- Track all serious adverse events and medication errors potentially related to Kineret® and report these to FDA. Complete and submit a MedWatch form or complete and submit FDA Form 3500 by fax (1-800-FDA-0178). Submitted reports must state, "Kineret® use for COVID-19 under EUA" at the beginning of the question "Describe Event" for further analysis. ***Federal, Tribal, and Urban programs are all encouraged to put "IHS" into field #26 of the form.***
- Ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.
- Maintain records regarding the dispensing and administration of Kineret® for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered)
- Ensure that any records associated with this EUA are maintained until notified by Sobi (manufacturer) and/or FDA. Such records will be made available to Sobi, HHS, and FDA for inspection upon request.
- Report therapeutics information and utilization data as directed by HHS.

References:

1. Food and Drug Administration. FDA Roundup: November 15, 2022. Released November 15, 2022.
2. Food and Drug Administration. Kineret Letter of Authorization. Issued November 8, 2022.
3. Food and Drug Administration. Kineret: FACT SHEET FOR HEALTHCARE PROVIDERS. Released November 8, 2022.
4. Food and Drug Administration. Kineret: FACT SHEET FOR PATIENTS, PARENTS & CAREGIVERS. Released November 2022.
5. Food and Drug Administration. FAQs on the Emergency Use Authorization of Kineret. Released November 8, 2022.