FACT SHEET FOR HEALTH CARE PROVIDERS

EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 CONVALESCENT PLASMA FOR TREATMENT OF HOSPITALIZED PATIENTS WITH COVID-19

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product high titer COVID-19 convalescent plasma to treat hospitalized patients with COVID-19. Available evidence suggests potential benefit is associated with transfusion of high titer COVID-19 convalescent plasma early in the course of disease and those hospitalized with impaired humoral immunity. Transfusion of COVID-19 convalescent plasma to hospitalized patients late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

The information in this Fact Sheet is the minimum information necessary to inform you of the significant known and potential risks and benefits of the emergency use of COVID-19 convalescent plasma.

As the health care provider administering COVID-19 convalescent plasma, you must provide recipients with the **Fact Sheet for Patients/Caregivers** and must communicate the following information to the recipients:

1. FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product

2. The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma

3. The significant known and potential risks and benefits of COVID-19 convalescent plasma and the extent to which such risks and benefits are unknown

4. Information on available alternative treatments and the risks and benefits of those alternatives.

If providing this information will delay the administration of COVID-19 convalescent plasma to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after convalescent plasma is administered.

For information on clinical trials that are testing the use of COVID-19 convalescent plasma for COVID-19, please see www.clinicaltrials.gov.

INTENDED USE

The EUA for COVID-19 convalescent plasma authorizes the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. This EUA is

based on historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, preclinical evidence, results from clinical trials of convalescent plasma and related passive immune therapies conducted during the current outbreak, and data obtained from the National Expanded Access Program (EAP) sponsored by the Mayo Clinic.

Data suggest that use of COVID-19 convalescent plasma with high antibody titer may be effective in treating hospitalized patients with COVID-19 when administered early in the course of disease or when administered to patients with impaired humoral immunity. Early in the course of disease generally means prior to respiratory failure requiring intubation and mechanical ventilation. Limited clinical evidence suggests the potential therapeutic window following symptom onset may be longer in patients with suppressed or deficient humoral immunity.

FDA will continue to evaluate this authorization based on additional data that become available.

Given that the clinical evidence supporting this EUA remains limited, data from additional randomized, controlled trials are needed. Convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Ongoing clinical trials of convalescent plasma should not be amended based on the issuance of the EUA. Providers are encouraged to enroll patients in those ongoing clinical trials.

PRODUCT DESCRIPTION

High titer COVID-19 convalescent plasma is human plasma collected by FDA registered or licensed blood establishments from individuals whose plasma contains high levels of anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and are qualified. Convalescent plasma is qualified and labeled as having high titer anti-SARS-CoV-2 antibodies based on testing accepted by FDA under this EUA. Qualification of COVID-19 convalescent plasma as high titer is based on serologic correlates of neutralizing activity, i.e., the ability of the donor antibodies to block infection by reference strains of the SARS-CoV-2 virus in laboratory tests.

DOSAGE, ADMINISTRATION, AND STORAGE OF COVID-19 CONVALESCENT PLASMA

Dosage

Health care providers will administer high titer COVID-19 convalescent plasma according to standard hospital procedures and institutional medical and nursing practices.

Clinical dosing may first consider starting with one high titer COVID-19 convalescent plasma unit (about 200 mL), with administration of additional convalescent plasma units based on the prescribing physician’s medical judgment and the patient’s clinical response.

Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.

Administration
Administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma (http://www.aabb.org/tm/coi/Documents/coi1017.pdf).

Storage
COVID-19 convalescent plasma, may be stored frozen at -18°C or colder, and has an expiration date one year from the date of collection. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

DRUG INTERACTIONS
COVID-19 convalescent plasma may be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.

SIDE EFFECTS, RISKS, BENEFITS, AND RISK-BENEFIT ASSESSMENT

Side Effects
Known side effects and hazards associated with plasma transfusion include transfusion-transmitted infections (e.g. HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described. Additional information on risks of plasma can be found in the AABB Circular of Information (http://www.aabb.org/tm/coi/Documents/coi1017.pdf).
Adverse event monitoring in studies of COVID-19 convalescent plasma has shown low overall rates of serious adverse events, and risks do not appear to exceed those associated with plasma transfusion in general.

Risks
A theoretical risk of administration of convalescent plasma is the phenomenon of antibody-dependent enhancement of infection (ADE). ADE has been described in other viral infections, such as dengue, and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms of ADE have been proposed, including the theoretical concern that antibodies to one type of coronavirus could enhance infection to another strain. Preparations with high titers of antibody against the same virus strain are thought to be less likely to cause ADE.

Another theoretical risk is that antibody administration may attenuate the immune response and make patients more susceptible to re-infection.

Benefits
COVID-19 is a serious and potentially fatal or life-threatening human disease. The potential benefits of COVID-19 convalescent plasma therapy could include improvement in symptoms, reduced need for supplemental oxygen and mechanical ventilation, and reduced mortality. Support for the safety and effectiveness of COVID-19 convalescent plasma is derived from past human experience with convalescent plasma, evidence of preclinical safety and efficacy in

animal models, published studies on the safety and efficacy of COVID-19 convalescent plasma and related passive immune therapies in COVID-19 patients. Available evidence suggests that COVID-19 convalescent plasma with high antibody titer may be effective in reducing disease progression and reducing mortality in hospitalized patients with COVID-19 when administered early in the course of disease, and those hospitalized with impaired humoral immunity.

Risk-Benefit Assessment
Based on the totality of scientific evidence available at this time, the known and potential benefits of high titer COVID-19 convalescent plasma outweigh the known and potential risks when administered early in the course of disease, and those hospitalized with impaired humoral immunity. Transfusion late in the course of illness (e.g., following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit. Limited clinical evidence suggests the potential therapeutic window may be longer in patients with suppressed or deficient humoral immunity.

USE IN SPECIFIC POPULATIONS

Pediatric
Safety and effectiveness of COVID-19 convalescent plasma in the pediatric population has not been evaluated. The decision to treat patients <18 years of age with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

Geriatric
In the National Expanded Access Program sponsored by the Mayo Clinic, 69,811 patients were treated as of August 20, 2020. Preliminary analyses of the first 20,000 patients indicated that 5,423 (27.1%) were 60-69 years of age, 4,114 (20.6%) were 70-79 years of age, and 2,568 (12.8%) were 80 years of age or older. Although adverse event rates in the geriatric subgroup have not yet been provided, the rates in the overall population for the individual events of mortality within 4 hours, TACO, TRALI, severe allergic transfusion reaction, thrombotic/thromboembolic complication, sustained hypotension, and cardiac events were ≤ 0.37%.

Pregnancy
Safety and effectiveness of COVID-19 convalescent plasma in pregnancy has not been evaluated. It should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Nursing Mothers
It is not known whether or not transfused anti-SARS-CoV-2 antibodies are excreted in human milk. The safety and effectiveness of COVID-19 convalescent plasma in nursing mothers has not been evaluated. The decision to treat nursing mothers with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

REPORTING ADVERSE EVENTS

Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.

As a health care provider, you must comply with the mandatory requirements of the EUA.

FDA-APPROVED ALTERNATIVES

As of the date of this fact sheet, one drug has been approved by FDA for the treatment of certain hospitalized patients with COVID-19 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf), but it is not considered an adequate alternative for the treatment of hospitalized patients with COVID-19. There are no other drugs or other therapeutics approved by the FDA to prevent or treat COVID-19 infection. There are EUAs for other COVID-19 treatments (visit https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs). The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

COUNTERMEASURES INJURY COMPENSATION PROGRAM

The Countermeasures Injury Compensation Program (CICP) is a federal program created to help pay for related costs of medical care and other specific expenses for eligible people seriously injured by the administration or use of certain medical countermeasures. Medical countermeasures may include vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a current, or potential future, public health emergency or a security threat. For more information about CICP, visit http://www.hrsa.gov/cicp/ or call: 1-855-266-2427.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the U.S. Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued an EUA for the unapproved product, COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19. FDA issued this EUA requested by ASPR and based on their submitted data and other available data about COVID-19 convalescent plasma.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that high titer COVID-19 convalescent plasma may be effective for the treatment of COVID-19 in hospitalized patients early in the course of disease and those hospitalized with impaired humoral immunity as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for COVID-19 convalescent plasma will end when the Secretary determines that the circumstances justifying the EUA no longer exist, if additional data were to become available to no longer support the product's use under an EUA, or when there is a change in the approval status of the product such that an EUA is no longer needed.