GUIDANCE FOR HEALTH CARE PROVIDERS

EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 CONVALESCENT PLASMA FOR TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS AND INTERIM GUIDANCE (90 DAYS) FOR COVID-19 CONVALESCENT PLASMA WITH UNKNOWN ANTIBODY TITER

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product COVID-19 convalescent plasma (CCP) to treat hospitalized patients with COVID-19. The FDA EUA requires that the CCP titers of units be defined as "High" or "Low" titer CCP units. Presently, the CCP in Medstar blood bank inventory has been defined as qualitatively positive for antibody but the amount (titer) is not known. It is not under EUA but FDA allows for the use of this CCP titer unknown for hospitalized COVID-19 patients for the next 90 days without an IND. Thus, the EUA FACT sheet will not apply to our current CCP units which are NOT labeled as "High" or "Low" titer. A Medstar patient informational FACT sheet for "non-EUA" may be given to patients to assist with informed consent and the Provider must include language (below) on the Medstar standard transfusion consent form to administer CCP of unknown titer.

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/Care givers 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. CCP that is available in Medstar inventory presently is of unknown titer.

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

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

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

COVID-19

Per FDA, the fact that this is an investigational product must be documented on the transfusion informed consent.
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 COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. This applies to CCP of unknown titer as well. This EUA is based on historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Data suggest that use of COVID-19 convalescent plasma with high antibody titer may be effective in reducing mortality in hospitalized patients with COVID-19. Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by a test described below are considered "COVID-19 Convalescent Plasma of Low Titer" and are authorized for use (see Product Description). Health care providers can decide whether to use these units based on an
individualized determination of potential benefit: risk. FDA will continue to evaluate this authorization based on additional data that become available. Current evidence also suggests that benefit is most likely in patients treated early in the course of the disease.

Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs 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

COVID-19 convalescent plasma is human plasma collected by FDA registered blood establishments from individuals whose plasma contains 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.

Units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma are considered Low Titer COVID-19 Convalescent Plasma and must be labeled accordingly. These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of benefit: risk. FDA will continue to evaluate this authorized use based on additional data that become available.

FDA has considered the large inventory of CCP which contains anti-SARS-CoV-2 antibodies for which titers are unknown. FDA permits the transfusion of these CCP units until December 1, 2020 at which time transfusion of these CCP units would require an IND.

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

Dosage

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

Clinical dosing may first consider starting with one 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 /heart failure or End Stage Renal Disease 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).

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 in COVID-19 patients including from the National Expanded Access Treatment Protocol sponsored by the Mayo Clinic (EAP). A report of adverse events in the initial population of 20,000 subjects in the EAP found low overall rates of serious adverse events. Analysis of over 35,000 transfused patients in the EAP study found a dose-response between antibody level and reduction in mortality.

Available evidence suggests that COVID-19 convalescent plasma with high antibody titer may be effective in reducing mortality in hospitalize d patients with COVID-19. Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by a test found acceptable for this purpose by FDA (see Product Description) are considered Low Titer COVID- 19 Convalescent Plasma and are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of patient benefit: risk. There remain many UNKNOWN Titer COVID- 19 Convalescent Plasma units in inventory and these products will be labeled with a tie-tag as such.

Risk-Benefit Assessment
Based on the totality of scientific evidence available at this time, the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks.

Informed Consent for use of COVID-19 CONVALESCENT PLASMA

After risks, benefits, alternatives and questions have been addressed, the prescribing provider must write on the standard transfusion consent form:

"The patient/caregiver was informed about the investigational nature of COVID Convalescent Plasma and were given the opportunity to ask questions. They were informed that the amount of anti-COVID antibodies present in the plasma is unknown at this time."

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 Treatment Protocol 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

There are no 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://clinicaltria ls.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 COVID-19 convalescent plasma may be effective for the treatment of COVID-19 in hospitalized patients 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.