What’s Changed this version:
Only high titer units of COVID-19 Convalescent Plasma (CCP) are allowed to be administered under the revised Emergency Use Authorization (EUA) effective 2/4/2021. Provides two methods to provide non-titer labeled CCP outside of the new EUA (which is currently the only CCP currently available from many blood product suppliers). Responds to frequently asked questions about the transition to the new EUA requirements.

Introduction

The U.S. Food and Drug Administration (FDA), a key participant in the exploration of potential therapies to fight the SARS-CoV-2 (COVID-19, the novel Coronavirus) pandemic, has investigated the use of COVID-19 convalescent plasma (CCP), an unapproved biological product containing antibodies collected from recovered individuals who previously tested positive for COVID-19. Data from the clinical trials has proven promising for patients who meet specified criteria and who receive high titer units.

Prior to 8/23/2020, convalescent plasma was administered only by organizations who had enrolled in clinical trials, most notably through the Mayo Clinic Expanded Access Protocol (EAP) or through a single patient emergency IND (eIND) application. On 8/23/2020 the FDA issued an Emergency Use Authorization (EUA) for administration of CCP to any hospitalized COVID-19 patient who meets the criteria to receive the product, even if the organization had not previously enrolled in a clinical trial.

Plasma donations must be tested, per the EUA, using an FDA approved test on an FDA approved platform as outlined in the revised EUA dated Feb. 4, 2021, for antibodies to determine suitability before release. Only units labeled as high titer are permitted for administration under the revised EUA.

Use of Convalescent Plasma

CCP, as with all blood products, is limited in supply and is an option for patients with severe disease. Consider performing a risk-benefit assessment of the patient prior to prescribing to conserve resources.

Refer to the COVID-19 Pharmacotherapy Treatment Guidance for patient selection and ordering information.

COVID-19 Convalescent Plasma (CCP) Revised Emergency Use Authorization (EUA)

Summary

Overview

- The full CCP Emergency Use Authorization can be found on the FDA website at https://www.fda.gov/media/141477/download
- COVID-19 Convalescent Plasma (CCP) should not be considered a new standard of care for the treatment of patients with COVID-19.
- It is used for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization.
Testing

- Donations: Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable for Convalescent Plasma donation (21 CFR 630.30).
  - Plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release.

Tested Units and Labeling:

On Feb. 4, 2021, the Food and Drug Administration (FDA) issued updated emergency use authorization (EUA) for convalescent plasma as a COVID-19 treatment, reflecting new data regarding its efficacy and application. As such, the FDA also updated its Healthcare Provider and Patient and Parent/Caregiver Fact Sheets. If high titer CCP is available, these fact sheets are to be used and the patient or parent/caregiver provided a fact sheet prior to receiving the CCP.


The new EUA for COVID-19 convalescent plasma limits the authorization to the use of high titer COVID-19 convalescent plasma only for the treatment of hospitalized patients with COVID-19 early in the disease course and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response. According to the latest data, plasma with low levels of antibodies has not been shown to be helpful in COVID-19.

The use of low or unlabeled titer COVID-19 convalescent plasma (CCP) is no longer authorized under the 2/4/2021 EUA as additional data from clinical trials, including randomized, controlled trials, have not shown evidence to demonstrate that low titer convalescent plasma may be effective in the treatment of hospitalized patients with COVID-19.

Suppliers of COVID-19 convalescent plasma, e.g., American Red Cross, have continued to work towards analyzing donated plasma to meet FDA’s specification of high titer but are not at a point at which units supplied to many ministries comply with the updated EUA. In guidance from the FDA to blood product suppliers issued on Jan. 15, 2021, the Red Cross notes the deadline for labeling CCP in accordance with the EUA requirements (i.e., high titer) was extended to May 31, 2021. The American Red Cross plans to be fully compliant with the requirements well before this date. At this time however Red Cross has not started labeling with a high titer designation. This means many ministries Transfusion Services (Blood Bank) have CCP that is unlabeled. To continue to serve patients in the interim we recommend providers follow one of the approaches outlined below:

If a provider determines a patient can benefit from CCP therapy and the only units available are unlabeled as to level of antibody titer, follow one of two options:

a) Use of CCP under FDA discretionary enforcement:

   NOTE: This option is available only until May 31, 2021, and may be removed sooner if the FDA revises the Jan. 15, 2021, blood products guidance. If high titer supplies are available to the provider, the high titer CCP should be used.

   Recognizing the immediate need for convalescent plasma to treat patients early in the course of their COVID-19, FDA is exercising temporary enforcement discretion regarding the IND
requirements (below) for the use of CCP. FDA intends to exercise this temporary enforcement discretion provided the following circumstances are present:

A. The treating health care provider obtains adequate informed consent from the patient or his or her legally authorized representative. Use the informed consent template on COVID-19 website under Clinical Guidance as well as fact sheets that relate to unlabeled CCP.
   - Convalescent Plasma Consent Template (trinity-health.org)
   - Fact Sheet for Patients and Parents/Caregivers – EUA for COVID-19 Convalescent Plasma to Treat Hospitalized Patients (trinity-health.org)
   - Fact Sheet for Health Care Providers – EUA for COVID-19 Convalescent Plasma to Treat Hospitalized Patients (trinity-health.org)

B. The investigational convalescent plasma is collected by registered blood establishments from donors who meet all eligibility requirements and qualifications.

C. The container label of investigational convalescent plasma includes the following statement, “Caution: New Drug—Limited by Federal (or United States) law to investigational use” (21 CFR 312.6(a))

b) Investigational new drug (IND):

Until May 31, 2021, most CCP should be given under option (a) Discretionary Enforcement.

This option is available if supplies of high titer are not available and likely a pathway available for any remaining, unlabeled CCP after May 31, 2021. An IND application for expanded access is an alternative for use of investigational convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials.

A. Single Patient IND for Emergency Use

Given the public health emergency that the COVID-19 pandemic presents, FDA is continuing to facilitate access to investigational convalescent plasma through the process of a physician requesting a single patient IND for an individual patient with serious or life-threatening COVID-19 under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met. Note, in such cases, a licensed physician seeking to administer investigational convalescent plasma to an individual patient must request the IND using the following steps:

- To obtain a single patient IND for emergency use, the requesting physician may contact FDA by completing Form FDA 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov. CBER requests that all forms be filled out electronically to facilitate rapid review.
- For requests when the provider is unable to complete and submit Form FDA 3926 due to extenuating circumstances, or in the case of a medical emergency between the hours of 8 p.m. and 8 a.m. Eastern Time (ET), i.e., when authorization and issuance of an IND number is needed before 8 a.m. ET the next morning, the provider should contact FDA’s Office of Emergency Operations at 1-866-300-4374
Frequently Asked Questions about the new Emergency Use Authorization (EUA):

**How have we been administering COVID Convalescent Plasma (CCP) up until this time?**

- Previously providers at ministries have been ordering CCP under the prior Aug. 23, 2020, EUA that did authorize administration of CCP that lacked a label as high titer if the provider determined that the benefit outweighed the risk for the patient identified as eligible for CCP. Units under this were classified as **CCP of Low Titer**.
- Ministries that use the American Red Cross as their CCP provider have been providing CCP as an IND under the FDA’s discretionary enforcement policy.

**How does the FDA want us to handle the transition if our blood provider is not able to label the units or we currently have non-labeled units in inventory?**

- The new EUA does not address transition issues
- Trinity Health has contacted the FDA and their representative confirmed that providers can order unlabeled CCP for their patients and FDA is not enforcing its normal requirements of investigational new drug (IND) during the transition to sustained availability of high titer CCP.
- If patient meets criteria for CCP, consult with transfusion services to discuss what units are currently available at your ministry. If high titer labeled units are available that is preferred and provide updated fact sheet to the patient and obtain their consent. If only unlabeled CCP is available, follow the discretionary enforcement option above.

On Feb. 9, 2021, the American Red Cross released the following guidance:

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Dear Transfusion Service Partner,

As you know, the situation with COVID-19 Convalescent Plasma (CCP) is continuously evolving. On February 4, 2021 the FDA announced a revision to its Emergency Use Authorization (EUA) that changes the use of CCP. Under the revised terms of the EUA only units that qualify as “high-titer” as defined by specific assays can be labeled as CCP and these should be transfused to hospitalized COVID-19 patients who are early in the course of the disease. According to the FDA, there is no specific cut off in the number of days post-diagnosis that CCP can be transfused, however the earlier the better. The EUA has suggested that patients in respiratory failure or on a ventilator, unless with compartmentalized humoral immunity, would still likely benefit from CCP treatment. In addition to the announcement, FDA also issued a revised Fact Sheet for Health Care Providers. These documents provide further detail on the rationale for the changes as well as updated CCP transfusion guidelines. The deadline for enforcement of the EUA requirements has been extended twice, most recently to May 31, 2021.

The Red Cross currently distributes investigational CCP labeled under IND and not labeled with any FDA designations. We will continue to distribute the investigational product as we actively develop our transition plan. Based on the FDA guidance, we are working to implement an allowed for testing methodology and transition to “high-titer” labeling of CCP as early as possible. Hospitals may continue to transfuse CCP labeled under IND until the enforcement date of May 17. However, FDA is encouraging industry transition to “high-titer” CCP as soon as operationally feasible. The Red Cross expects to begin providing EUA-compliant “high-titer” CCP well in advance of this date and will notify you as soon as we are ready to implement this change.

As a reminder, all units of CCP are currently funded by BARDA and continue to be distributed free of charge. Our contract with BARDA expires in March, however, given the expected remaining inventory, we do not expect to begin charging for CCP until some point in April. We will provide more information on this change away as we draw closer to implementation.

Thank you for your partnership in serving patients in need.

Pamela P. Young, M.D., Ph.D.
Chief Medical Officer

American Red Cross
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Can I still provide CCP if I only have units without a titer label?

- Yes, since the timely administration of CCP is important for patient treatment, continue to administer CCP units for patients who meet eligibility criteria.

What if I have high titer labeled units?

- Administer the CCP under the new EUA using the forms linked from this document.

What do I do if I have low-titer units?

- The FDA’s standpoint is that it wants patients to receive high-titer CCP. When asked for clarity about low titer units, it pointed out that CCP units can continue to be issued under the IND (which implies low titer units), or that low titer units can be relabeled as Fresh Frozen Plasma/Plasma frozen within 24 hours after phlebotomy (FFP/PF24).

- Local blood bank medical directors should be aware of the issue and make a decision with their bedside teams on the best approach. Importantly, if an in-date and otherwise appropriate for transfusion CCP unit is going to be discarded, the ministry should first contact their blood supplier. All CCP units continued to be paid by the Biomedical Advanced Research and Development Authority (BARDA), part of the HHS Office of the Assistant Secretary for Preparedness and Response (at least through March), and BARDA has set rules for how disposed units should be handled.

What if I have both high titer and unlabeled units without a titer designation?

- Administer the high titer units first following the new EUA protocol using the forms linked within this guide.

What forms do I use for COVID-19 Convalescent Plasma (CCP) administration?

- It depends on what type of CCP your ministry currently has available. See the table below for Fact Sheet and consent information and location.

<table>
<thead>
<tr>
<th>CCP Titer Label</th>
<th>Non-labeled Units</th>
<th>High Titer Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authorization Type</td>
<td>Discretionary enforcement option, OR Individual patient Investigation New Drug (IND) option</td>
<td>New, 2/4/21, Emergency Use Authorization</td>
</tr>
<tr>
<td>Fact Sheets to Use</td>
<td>Use the Fact Sheets (English and Spanish) that you’ve been using since late August - currently available on the Trinity Health Pulse COVID-19 website under Treatments Clinical Guidance (trinity-health.org)</td>
<td>Use the Fact Sheets that are included with this document. CCP Fact Sheet for Health Care Providers 02_04_2021 CCP Fact Sheet for Patients and Parents/Caregivers 02_04_2021</td>
</tr>
<tr>
<td>Consent Forms</td>
<td>Use the special CCP consents (English and Spanish) that you’ve been using since late August – currently available on the Trinity Health Pulse COVID-19 website Clinical Guidance (trinity-health.org)</td>
<td>Use your ministry’s blood bank consent forms and indicate the product as COVID-19 Convalescent Plasma</td>
</tr>
</tbody>
</table>
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.

Disclosures

- COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:
    - Changes to the authorized Fact Sheets may be requested by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR)

Blood Bank Requirements

A. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.
B. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18°C or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.
C. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).
D. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.

Hospitals Requirements

A. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to health care providers and to patients and caregivers, respectively, through appropriate means.
B. The authorized COVID-19 convalescent plasma must be stored frozen at -18°C or colder. Once thawed and refrigerated, the authorized COVID-19 convalescent plasma must be used within 5 days for patient transfusion.
C. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for
Health Care Providers. 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.

D. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, 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).

E. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.

Printed Matter, Advertising, and Promotion

All descriptive printed matter, including advertising and promotional material, relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:

- COVID-19 convalescent plasma has not been approved or licensed by FDA;
- COVID-19 convalescent plasma has been authorized by FDA under an EUA;
- COVID-19 convalescent plasma is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.


Administration

- Utilize organizational policy for administration of blood products.
- An order for convalescent plasma is required.
- The patient should be consented for convalescent plasma administration and provided the Fact Sheet for Patients and Parents/Caregivers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients.

Refer to the COVID-19 Pharmacotherapy Treatment Guidance for administration instructions.

Adverse Reactions Reporting

See COVID-19 Convalescent Plasma (CCP) Emergency Use Authorization (EUA) Summary above, which addresses the Hospital Requirements (C) for adverse effects reporting (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfdocs/cfdocs/CFRSearch.cfm?fr=606.170)

Provider Documentation Requirements

High Titer Units

Health care providers should read the Fact Sheet for Healthcare Providers developed by the FDA prior to ordering COVID-19 Convalescent Plasma. This document is available for download from the FDA at Fact Sheet for Health Care Providers COVID-19 Convalescent Plasma.
Prior to CCP administration, patients or caregivers should be given the Fact Sheet for Patients and Caregivers and must consent to treatment with COVID-19 Convalescent Plasma. The document is available for download from the FDA at Fact Sheet for Patients and Parents/Caregivers COVID-19 Convalescent Plasma.

The patient or parent/caregiver must sign a consent to receive COVID-19 Convalescent Plasma (CCP). Use your local ministry blood consent and indicate the product transfused as COVID-19 Convalescent Plasma.

Provider documentation should reflect that the patient has been provided with and accepts the disclosures as outlined in the Fact Sheet for Patients and Caregivers.

**Non-Titer labeled Units**

Health care providers should read the Fact Sheet for Healthcare Providers developed by the FDA prior to ordering COVID-19 Convalescent Plasma. This document is available for on the Trinity Health Pulse Website at Fact Sheet for Patients and Parents/Caregivers – EUA for COVID-19 Convalescent Plasma to Treat Hospitalized Patients (trinity-health.org)

Prior to CCP administration, patients or caregivers should be given the Fact Sheet for Patients and Caregivers and must consent to treatment with COVID-19 Convalescent Plasma. The document is available for download on the Trinity Health Pulse website at Fact Sheet for Patients and Parents/Caregivers – EUA for COVID-19 Convalescent Plasma to Treat Hospitalized Patients (trinity-health.org)

The patient or parent/caregiver must sign a consent to receive COVID-19 Convalescent Plasma (CCP). A modified consent for non-titer labeled units can be found on the Trinity Health Pulse website at Convalescent Plasma Consent Template (trinity-health.org)

Provider documentation should reflect that the patient has been provided with and accepts the disclosures as outlined in the Fact Sheet for Patients and Caregivers.