COVID-19 SUPPLEMENT | VOLUME 10 | MAY 2020

MEDICATION SAFETY IN SECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

REMDESIVIR: EMERGENCY USE AUTHORIZATION FOR POTENTIAL COVID-19 TREATMENT; LIMITED DATA AVAILABLE

FDA Issues EUA

FDA has issued an emergency use authorization (EUA) for the investigational antiviral remdesivir in patients with COVID-19. Under this EUA, the unapproved product can be administered by health care providers to treat hospitalized patients with suspected or laboratory-confirmed COVID-19 that is severe. Severe disease is defined as low blood oxygen levels (<94%), the need for oxygen therapy, or intensive respiratory support (i.e., mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).

The EUA was based on a clinical trial shown to shorten the time to recovery in some patients. The ACTT trial (Adaptive COVID-19 Treatment Trial) is an ongoing phase 3, double-blind, placebo-controlled trial of hospitalized patients with severe COVID-19 pneumonia, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Patients must have infiltrates on X-ray, require oxygen or ventilatory support or have room air oxygen saturation less than 94%. Preliminary results suggest that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (11 days for patients treated with remdesivir versus 15 days for those who received placebo, $p<0.001$). Results also indicate numerically lower mortality without statistical significance (8.0% for the remdesivir group versus 11.6% for placebo, $p=0.059$). Treatment in this study consists of 200 mg of remdesivir on the first day of enrollment followed by 100 mg per day for nine subsequent days of hospitalization or placebo. Final results including baseline demographics of the groups and details of the primary and secondary analyses are still forthcoming. Based on these data, a new NIAID trial, named ACTT2, will look at remdesivir alone versus remdesivir plus baracitinib to assess whether adding an anti-

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NEWSWORTHY...

from the pbm

- VHA PBM Information on investigational and off-label treatment of COVID-19 document - 05/07/2020
- Hydroxychloroquine/Chloroquine and Risk of Use Outside Hospital or Clinical Trial Settings - National PBM Bulletin - 04/24/2020
- HCQ and CQ Safety for COVID-19 Frequently Asked Questions AMENDMENT- 04/23/2020 – FAQ Sheet AMENDMENT

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VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

EDITOR-IN-CHIEF

Marie Sales, Pharm.D.
VA Pharmacy Benefits Management Services [PBM] & Center for Medication Safety [VA MedSAFE]; 1st Avenue—1 Block North of Cermak Road | Building 37; Room 139 | Hines, Illinois | 60141;
www.pbm.va.gov

NEWSWORTHY...

from the fda

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COVID-19 DISEASE

Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Additional Safety Protections Pertaining to SARS-CoV-2 and COVID-19

03/23/2020

Studies suggest that SARS-CoV-2 ribonucleic acid (RNA) and/or SARS-CoV-2 virus can be present in stool of infected individuals.[1-3] FDA warns that use of fecal microbiota for transplantation (FMT) to treat Clostridium difficile (C. difficile) infection in patients who have not responded to standard therapies may have the potential to transmit SARS-CoV-2, although the risk of such transmission is unknown.[4] To address the risk, stool used for FMT should have been donated before December 1, 2019. If stool used for FMT is donated after December 1, 2019, additional protective measures to take include:

- Donor screening with questions directed at identifying donors who may be currently or recently infected with SARS-CoV-2;
- Testing donors and/or donor stool for SARS-CoV-2, as feasible;
- Development of criteria for exclusion of donors and donor stool based on screening and testing; and
- Informed consent that includes information about the potential for transmission of SARS-CoV-2 via FMT, including FMT prepared from stool from donors who are asymptomatic for COVID-19.

REFERENCES:

[1] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H, Evidence for gastrointestinal infection of SARS-CoV-2, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.02.055External Link Disclaimer

[2] Tang A, Tong Z-d, Wang H-l, Dai Y-x, Li K-f, Liu J-n, et al. Detection of novel coronavirus by RT-PCR in stool specimen from asymptomatic child, China. Emerg Infect Dis. (2020), https://doi.org/10.3201/eid2606.200301External Link Disclaimer from https://wwwnc.cdc.gov/eid/article/26/6/20-0301_article

[3] Wang, W, Xu, Y, Gao, R, et al., Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA (2020), https://doi.org/10.1001/jama.2020.3786External Link Disclaimer

[4] Gu J, Han B, Wang J, COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.02.054

Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation - Screening Donors for COVID-19 and Exposure to SARS-CoV-2 and Testing for SARS-CoV-2

04/09/2020

A previous safety alert addressed the potential risk of transmission of SARS-CoV-2 virus via fecal microbiota for transplantation (FMT). At that time, FDA determined the need for additional protections for any use of FMT, whether under an Investigational New Drug Application (IND) on file with the FDA or under FDA's enforcement discretion policy. FDA is providing an update on these additional protections, which includes no clinical use of FMT product manufactured from stool donated on or after December 1, 2019, until the following measures are implemented:

1. Stool donor screening.
   - Assess whether the donor was diagnosed with laboratory-confirmed SARS-CoV-2 infection; experienced symptoms of COVID-19 (e.g., fever, cough, shortness of breath) not explained by another diagnosis; or was exposed to a suspected or confirmed case of COVID-19 or SARS-CoV-2 infection since December 1, 2019.
   - If SARS-CoV-2 infection or exposure is suspected or confirmed, exclude donor from further donations and exclude from clinical use any FMT product manufactured from stool donated by the affected donor beginning 4 weeks prior to the date of infection/exposure.
2. Testing stool donation or stool donor for SARS-CoV-2 virus or RNA.
   - Testing approaches might include: upper respiratory specimens (e.g., nasal swabs) or other specimens (e.g., rectal swabs or stool donations).
   - If SARS-CoV-2 is detected, exclude donor from further donations and exclude from clinical use any FMT product manufactured from stool donated by the affected donor beginning 4 weeks prior to the first positive test.
3. As part of the informed consent process, communicate to the FMT recipient that:
   - Healthy, asymptomatic stool donors may potentially be infected with SARS-CoV-2;
   - Testing approach and other strategies are used to mitigate the risk of SARS-CoV-2 transmission; and
   - Limitations of testing and risk mitigation strategies.

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REMDESIVIR: EMERGENCY USE AUTHORIZATION FOR POTENTIAL COVID-19 TREATMENT; LIMITED DATA AVAILABLE

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inflammatory agent to the remdesivir regimen can provide additional benefit for patients.

Evidence in the literature on the use of remdesivir for treatment of COVID-19 is limited. An uncontrolled compassionate use trial of the drug observed clinical improvement in 36 of 53 patients (68%); 25 patients (47%) were discharged; and 7 patients (13%) died. The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. However, this study lacked a control group making drug effect difficult to ascertain. Findings from a placebo-controlled trial in China of 237 patients showed remdesivir was not associated with statistically significant clinical benefits in the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo. Adverse events were reported in 66% of patients in the remdesivir group, of which the most commonly reported included constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin. Overall, serious adverse events were lower in remdesivir patients compared to those receiving placebo. Frequency of elevated transaminases appeared less with remdesivir (5%) than with placebo (12%). Rash and thrombocytopenia occurred with at least 4% greater incidence with remdesivir than placebo. However, more remdesivir patients than placebo patients discontinued because of adverse events (i.e., anorexia, nausea, and vomiting; aminotransferase or bilirubin increases; and worsened cardiopulmonary status). Of note, this trial was underpowered since sample size was not reached which led to early termination.

Additional preliminary data from the manufacturer includes an open-label, Phase 3 SIMPLE trial evaluating 5-day and 10-day dosing durations of remdesivir in 397 hospitalized patients with severe COVID-19 disease. Data did not show a difference in clinical improvement between a 5-day and a 10-day treatment course. Patients included had evidence of pneumonia and reduced oxygen levels that did not require mechanical ventilation upon study entry. The time to clinical improvement for 50% of patients was 10 days in the 5-day treatment group, and 11 days in the 10-day treatment group. More than half of patients in both treatment groups were discharged from the hospital by Day 14 (5-day: 60.0%, n=120/200 vs. 10-day: 52.3% n=103/197; p=0.14). At Day 14, 64.5% (n=129/200) of patients in the 5-day treatment group and 53.8% (n=106/197) of patients in the 10-day treatment group achieved clinical recovery. The most common adverse events occurring in approximately 10% of patients in the 5-day (n=200) and 10-day (n=197) treatment groups were nausea (10.0% [n=20] versus 8.6%, [n=17], respectively) and acute respiratory failure (6.0% [n=12] versus 10.7% [n= 21], respectively). Grade 3 or higher liver enzyme (ALT) elevations occurred in 7.3% (n=28/385) of patients, with 3.0% (n=12/397) of patients discontinuing remdesivir treatment due to elevated liver tests. An expansion up to 5,600 patients is in progress, including patients on mechanical ventilation. An exploratory analysis suggested that patients who received remdesivir within 10 days of the start of symptoms appeared to derive the most benefit. A second SIMPLE trial is ongoing to evaluate the safety and efficacy of the same dosing regimens of remdesivir plus standard of care compared with standard of care alone in 1,600 patients with moderate disease.

Mandatory Requirements for Remdesivir Administration Under EUA:

Under the EUA, health care facilities and health care providers are required to:

- Ensure awareness of the letter of authorization and the conditions for remdesivir emergency use, which consist of treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults hospitalized with severe disease defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring invasive mechanical ventilation or requiring ECMO.
- Provide authorized Fact Sheets to providers and to patients/caregivers, respectively, through appropriate means.
  - As part of the current EUA, FDA requires that the manufacturer provide fact sheets about remdesivir for health care providers and patients, which include information on potential adverse events such as increased levels of liver enzymes and infusion-related reactions (hypotension, nausea, vomiting, diaphoresis, and shivering) as well as dosing.
  - Fact sheets are available at the following links:
    - ⇒ https://www.fda.gov/media/137566/download
      Fact Sheet for Health Care Providers, Emergency Use Authorization (EUA) of Remdesivir (GS-5734™)
    - ⇒ https://www.fda.gov/media/137565/download
      Fact Sheet for Patients and Parent/Caregivers, Emergency Use Authorization (EUA) of Remdesivir for Coronavirus Disease 2019 (COVID-19)
- Communicate to patients and/or caregivers information consistent with the "Fact Sheet for Patients and Parents/Caregivers" prior to the patient receiving remdesivir. Documentation in the patient's medical record must confirm that the patient/caregiver was:
  - Given the Fact Sheet for Patients and Parents/Caregivers.
  - Informed of alternatives to receiving remdesivir and the risks and benefits of those alternatives.
  - Notified that FDA has authorized the emergency use of remdesivir, which is not an FDA approved drug.

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Getting the most from our safety surveillance

FDA CAUTIONS AGAINST USE OF HYDROXYCHLOROQUINE OR CHLOROQUINE FOR COVID-19 OUTSIDE OF THE HOSPITAL SETTING OR A CLINICAL TRIAL DUE TO CARDIAC RISK

FDA cautions that hydroxychloroquine (HCQ) or chloroquine (CQ), when used for COVID-19, should be limited to clinical trial settings or in-hospital use for certain patients under the Emergency Use Authorization (EUA). FDA became aware of increased use of HCQ and CQ through outpatient prescriptions. FDA reviewed case reports of serious cardiac adverse events and death in patients with COVID-19 receiving HCQ or CQ, either alone or combined with azithromycin or other QT prolonging medicines from the FDA Adverse Event Reporting System, the published medical literature, and the American Association of Poison Control Centers National Poison Data System. These adverse events occurred in hospital and outpatient settings and include QT interval prolongation, ventricular tachycardia and ventricular fibrillation, and in some cases, death associated with the use of HCQ or CQ to treat or prevent COVID-19.

HCQ and CQ have not been proven to be safe and effective for treating or preventing COVID-19. Recent studies suggest a lengthening effect on QT interval with the combined use of HCQ and azithromycin. Close supervision is strongly recommended due to potential for QT prolongation, other serious side effects, and drug-drug interactions with QT-prolonging medicines. Patients taking HCQ or CQ for FDA-approved indications to treat malaria or autoimmune conditions should continue taking their medicine as prescribed; the benefits outweigh risks at the recommended doses for these conditions.

Last month, VA PBM/MedSAFE issued a National PBM Bulletin addressing FDA's warning against use of hydroxychloroquine (HCQ) and chloroquine (CQ) for COVID-19 outside of the hospital or clinical trial settings (i.e., outpatient use unless in a clinical trial) due to risk of cardiotoxicity. Recommendations include:

- Use of HCQ/CQ for COVID-19 **should** be in the context of a clinical trial, **especially in unsupervised outpatient settings**. In the absence of such a trial, off-label use in hospitalized patients should occur using the best available information, **only AFTER** consultation with Infectious Diseases and/or other facility designated experts, **AND AFTER** evaluating the potential benefits and risks associated with the treatment, customized to the needs of the patient. Discussion of these risks/benefits should be in consultation with the patient, family, and in keeping with the PBM Document entitled: Pharmaceutical Use Outside of Approved Indications Guidance on "Off-Label" Prescribing (August 2013).
- Providers should monitor QTc at baseline and continue monitoring after start of HCQ or CQ.
- Providers should report any adverse drug events with the use of HCQ/CQ alone or those caused by drug-drug interactions by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800- FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).
- Additional safety information and monitoring recommendations for HCQ or CQ have been addressed in a "Frequently Asked Questions" document, which is available at: https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/FAQ%20SHEETS/HCQ%20and%20CQ%20%20Safety%20for%20COVID-19%20Frequently%20Asked%20Questions_Amendment_FINAL.pdf .

For further details, please refer to the National PBM Bulletin issued on April 24, 2020.

REFERENCE:
FDA Drug Safety Communication. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or . Accessed 4/24/2020.

GENERAL COVID –19 RESOURCES

Click on links below for more information:

- CDC Information on COVID-19 Disease for Healthcare Professionals
- CDC Clinical Care Information for Healthcare Professionals Regarding COVID-19
- CDC Information on Therapeutic Options for COVID-19 Patients
- World Health Organization Interim Guidance for Clinical Management of Severe Acute Respiratory Infection When COVID-19 is Suspected
- National Institutes of Health COVID-19 Treatment Guidelines
- Guidelines from the Infectious Diseases Society of America
- The American Society of Health-System Pharmacists evidence table of COVID-19 treatments

COVID-19 ORD NOTICES & GUIDANCE

VA Office of Research and Development (ORD) resources on COVID-19 are available at:

https://dvagov.sharepoint.com/sites/vacovhacomm/admin/projects/covid19/SitePages/ORD-Communications.aspx

This SharePoint site contains information and resources for VA research administrators, investigators and staff. Content continues to be updated as new information emerges. The direct link is only accessible internally within VA.

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- Advised that the patient or parent/caregiver has the option to accept or refuse remdesivir.
- Counselled on the significant known and potential risks and benefits of remdesivir, and the extent to which such risks and benefits are unknown.

- Monitor renal and hepatic parameters in accordance to the Fact Sheet for Health Care Providers:
  - Determine eGFR;
  - Hepatic laboratory testing in all patients prior to starting remdesivir and daily while receiving remdesivir.
- Track serious adverse events potentially associated with remdesivir use and report these to FDA in accordance with the Fact Sheet for Healthcare Providers.
  - The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and adverse events (death, serious adverse events) considered to be potentially related to remdesivir occurring during remdesivir treatment within 7 calendar days from the onset of the event.
  - The reports should include unique identifiers and the words "Remdesivir under Emergency Use Authorization (EUA)" in the description section of the report.
  - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" a statement "Remdesivir under Emergency Use Authorization (EUA)."
  - 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 disruption of the ability to conduct normal life functions; a congenital anomaly/birth defect; a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.
- Through a process of inventory control, maintain records regarding:
  - the dispensed authorized remdesivir (i.e., lot numbers, quantity, receiving site, receipt date);
  - product storage;
  - 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 Gilead and/or FDA. Such records will be made available to Gilead, HHS, and FDA for inspection upon request.

In addition to the above, providers should continue to report any adverse drug events with the use of remdesivir by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800- FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-_online.htm, or by mail). Reporting can help to identify serious and unexpected adverse events that have not been previously reported with remdesivir use given the limited experience with remdesivir at the recommended dose.

VA Distribution of Remdesivir Under EUA:

VA received a centralized supply of remdesivir and has been able to accommodate all requests for product to date. For sites that have patients who meet the EUA criteria for use of remdesivir, a patient specific order, which will be sent by UPS overnight, can be entered at the following link: https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/COVID/Lists/ROF/AllItems.aspx .

REFERENCES:

1. FDA News Release. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment . Accessed 5/1/2020.
2. NIH Clinical Trial shows remdesivir accelerates clinical recovery from advanced COVID-19. NIH Press release. 4/29/20. Accessed 4/30/20.
3. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for severe COVID-19. *N Engl J Med* 2020.Apr 10. Doi.10.1056/NEJMoa2007016
4. Wang Y, Zhang D, Du G et al. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial. *Lancet* 2020;S0140-6736 https://doi.org/10.1016/S0140-6736(20)31022-9
5. Gilead Press Release. Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients With Severe COVID-19. April 29, 2020. Available at: https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19 . Accessed 5/1/2020.
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