FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF HYDROXYCHLOROQUINE SULFATE SUPPLIED FROM THE STRATEGIC NATIONAL STOCKPILE FOR TREATMENT OF COVID-19
IN CERTAIN HOSPITALIZED PATIENTS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of hydroxychloroquine sulfate supplied from the Strategic National Stockpile to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.

This EUA is for the unapproved use of hydroxychloroquine sulfate supplied from the Strategic National Stockpile (SNS) to treat adults and adolescents who weight 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible

Hydroxychloroquine sulfate must be administered orally

To request chloroquine phosphate under Emergency Use Authorization (EUA):
Contact your Local or State Health Department

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** related to chloroquine phosphate.
See specific reporting instructions below.

The optimal dosing and duration of treatment is unknown.

The suggested dose under this EUA for hydroxychloroquine sulfate to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible, is 800 milligrams of hydroxychloroquine sulfate on the first day of treatment and then 400 milligrams daily for four to seven days of total treatment based on clinical evaluation.

The suggested dose and duration may be updated as data from clinical trials becomes available.

For information on clinical trials that are testing the use of hydroxychloroquine sulfate in COVID-19, please see www.clinicaltrials.gov.

INSTRUCTIONS FOR ADMINISTRATION

This section provides essential information on the unapproved use of hydroxychloroquine sulfate under this EUA in adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.

Please refer to this fact sheet for information on use of hydroxychloroquine sulfate under the EUA. Indication for COVID-19 is not part of the FDA-approved labeling but hydroxychloroquine sulfate information for other FDA-approved indications, including pharmacokinetics and safety profile information, other than dosing recommendations, may be found in an FDA-approved package insert at https://dailymed.nlm.nih.gov/dailymed/

The FDA-approved labeling does not include information regarding safety or effectiveness in COVID-19. Please refer to this fact sheet for information on use of hydroxychloroquine sulfate under the EUA and the above link for FDA-approved labeling for additional information.

Contraindications
Hydroxychloroquine sulfate is contraindicated in the presence of retinal or visual field changes of any etiology and in patients with known hypersensitivity to 4-aminoquinoline compounds. Hydroxychloroquine sulfate should not be used in patients with a prolonged QT interval at baseline or at increased risk for arrythmia. Health care providers should carefully review **Warnings** and **Drug Interactions** below before prescribing hydroxychloroquine sulfate.

Dosing
The optimal dosing and duration of treatment for COVID-19 is unknown.

The suggested dose under this EUA for hydroxychloroquine sulfate to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible, is 800 milligrams of hydroxychloroquine sulfate on the first day of treatment and then 400 milligrams daily for four to seven days of total treatment based on clinical evaluation.[1]

The suggested dose and duration may be updated as data from clinical trials becomes available.

Recommended Laboratory and Monitoring Procedures
A baseline electrocardiogram should be obtained to assess for QT interval prolongation and other abnormalities. Baseline evaluation of renal and hepatic function is recommended.

Warnings
Cardiac Effects: QT interval prolongation. Use with caution in patients with cardiac disease, QT prolongation, a history of ventricular arrhythmias, bradycardia, uncorrected potassium or magnesium imbalance, and during concomitant administration with QT interval prolonging drugs such as azithromycin and some other antibacterial drugs. Monitor the electrocardiogram during treatment.

[1] The dosage of hydroxychloroquine sulfate is often expressed in terms of equivalent hydroxychloroquine base. Each 200 milligram tablet of hydroxychloroquine sulfate is equivalent to 155 milligram base. The dosing suggested in the Fact Sheet is for hydroxychloroquine sulfate.

Myocarditis, pericarditis, and cardiomyopathy may increase risk for arrythmia. Monitor for cardiac injury.

Severe hypoglycemia: Hydroxychloroquine sulfate has been reported to decrease insulin clearance and resistance. Loss of consciousness in patients with or without the use of antidiabetic medications has been reported.

Hematologic effects: Hemolysis in G6PD deficient patients, pancytopenia, aplastic anemia and neutropenia have been reported.

Hepatic impairment: Since hydroxychloroquine sulfate is known to concentrate in the liver, it should be used with caution in patients with hepatitis, hepatic disease, alcoholism or in conjunction with known hepatotoxic drugs.

Renal impairment: Hydroxychloroquine sulfate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.[1]

Central nervous system effects: Hydroxychloroquine sulfate may increase the risk of convulsions in patients with a history of seizures. Acute extrapyramidal disorders may occur with hydroxychloroquine sulfate. Psychosis, delirium, agitation, confusion, suicidal behavior, and hallucinations may occur with hydroxychloroquine sulfate.

Worsening of Psoriasis and Porphyria: Use of hydroxychloroquine sulfate in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. Hydroxychloroquine sulfate should not be used in these conditions unless the benefit to the patient outweighs the potential risks.

Retinopathy: Retinal damage has been observed in some patients receiving long-term treatment with hydroxychloroquine sulfate.

Drug Interactions

Digoxin: Concomitant hydroxychloroquine sulfate and digoxin therapy may result in increased serum digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

Antacids and kaolin: Antacids and kaolin can reduce absorption of hydroxychloroquine sulfate; an interval of at least 4 hours between intake of these agents and hydroxychloroquine sulfate should be observed.

Cimetidine: Cimetidine can inhibit the metabolism of hydroxychloroquine sulfate, increasing its plasma level. Concomitant use of cimetidine should be avoided.

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[1] Some experts recommend a dose reduction of 50% for GFR < 10 mL/minute, hemodialysis, or peritoneal dialysis; no dose reduction is recommended if GFR $\geq$ 10 mL/minute.

Insulin and other antidiabetic drugs: As hydroxychloroquine sulfate may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or other antidiabetic drugs may be required.

Arrhythmogenic drugs: There may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine sulfate is used concomitantly with other arrhythmogenic drugs, such as amiodarone, azithromycin or moxifloxacin.

Ampicillin: In a study of healthy volunteers, hydroxychloroquine sulfate significantly reduced the bioavailability of ampicillin. An interval of at least two hours between intake of ampicillin and hydroxychloroquine sulfate should be observed.

Cyclosporine: After introduction of hydroxychloroquine sulfate, a sudden increase in serum cyclosporine level has been reported. Therefore, close monitoring of serum cyclosporine level is recommended and, if necessary, hydroxychloroquine sulfate should be discontinued.

Mefloquine: Co-administration of hydroxychloroquine sulfate and mefloquine may increase the risk of convulsions.

Praziquantel: In a single-dose interaction study, hydroxychloroquine sulfate has been reported to reduce the bioavailability of praziquantel.

Tamoxifen: Concomitant use of hydroxychloroquine sulfate with drugs known to induce retinal toxicity such as tamoxifen is not recommended.

Antiepileptics: The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine sulfate.

Usage in Pregnancy
In animal studies, embryo-fetal developmental toxicity was shown at doses approximately 3 to 16 times the maximum recommended therapeutic dose based on a body surface area comparison. Preclinical data showed a potential risk of genotoxicity in some test systems. In humans, at recommended doses for prophylaxis and treatment of malaria, observational studies as well as a meta-analysis, including a small number of prospective studies with hydroxychloroquine sulfate exposure during pregnancy, have shown no increase in the rate of birth defects or spontaneous abortions.

The individual benefit-risk balance should be reviewed before prescribing hydroxychloroquine sulfate in pregnant women.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider administering hydroxychloroquine sulfate, you should, prior to prescribing/dispensing in accordance with applicable state and local law, provide your patients with the Fact Sheet titled “Emergency Use Authorization (EUA) of Hydroxychloroquine Sulfate Fact Sheet for Patients and Parent/Caregivers” and communicate the following information to the patient:

1. That the Secretary of HHS has authorized emergency use hydroxychloroquine sulfate.

2. That the patient has the option to accept or refuse administration of hydroxychloroquine sulfate
3. The potential consequences of refusing hydroxychloroquine sulfate
4. The significant known and potential risks and benefits of hydroxychloroquine sulfate, as supplied under this EUA.
5. The alternative products that are available and their benefits and risks, including clinical trials.

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

MANDATORY REQUIREMENTS FOR HYDROXYCHLOROQUINE SULFATE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:
In order to mitigate the risks of using this approved product for an unapproved use under EUA and to optimize the potential benefit of hydroxychloroquine sulfate, the following items are required. Use of hydroxychloroquine sulfate under this EUA is limited to the following (all requirements **must** be met):

1. Adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.
2. As the health care provider, communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients and Parents/Caregivers" prior to the patient receiving hydroxychloroquine sulfate. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
    a. Given the Fact Sheet for Patients and Parents/Caregivers,
    b. Informed of alternatives to receiving authorized hydroxychloroquine sulfate, and
    c. Informed that hydroxychloroquine sulfate is an approved drug that is authorized for the unapproved use under this Emergency Use Authorization.
3. The prescribing health care provider and/or the provider's designee are/is to provide responses to requests from FDA for information about adverse events and medication errors following receipt of hydroxychloroquine sulfate.

4. The prescribing health care provider and/or the provider's designee are/is responsible for reporting medication errors and adverse events (death, serious adverse events*) occurring during hydroxychloroquine sulfate treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "**Hydroxychloroquine Sulfate Treatment under Emergency Use Authorization (EUA).**" in the description section of the report.

    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or

- By using a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form
- Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "**Hydroxychloroquine Sulfate Treatment under 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.

Additional Requirement for Use under this EUA

1. Additional requirements for reporting of patient outcomes, in addition to safety, may be required as a condition of use under this EUA.

APPROVED AVAILABLE ALTERNATIVES

There are no approved available alternative products. There is an EUA for treatment of the same population with chloroquine phosphate. Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared an emergency that justifies the emergency use of hydroxychloroquine sulfate supplied from the Strategic National Stockpile to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible. In response, the Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the unapproved use of the FDA approved product hydroxychloroquine sulfate supplied from the Strategic National Stockpile for adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom participation in a clinical trial is not available or participation is not feasible**.** As a health care provider, you must comply with the mandatory requirements of the EUA listed above.

FDA issued this EUA, requested by Biomedical Advanced Research and Development Authority (BARDA).

Although limited scientific information is available, it is reasonable to believe that hydroxychloroquine sulfate may be effective for treatment of adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible, 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. Serious adverse events related to the use of hydroxychloroquine sulfate must be reported to FDA through FDA's MEDWATCH Voluntary Online reporting www.fda.gov/medwatch/report.htm. Please include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the following statement: **Hydroxychloroquine Sulfate Treatment under Emergency Use Authorization (EUA).**

This EUA for hydroxychloroquine sulfate will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

Distributed by: Bruce Bethancourt, MD; Karen McConnell, PharmD; Ben Chaska, MD on behalf of the CommonSpirit Health System P & T Committee - April 1,2020

Source: FDA