May 28, 2020

Matthew V. Topic, Esq.
Loevy & Loevy
311 N. Aberdeen Street
Third Floor
Chicago, IL 60607
Via Email: foia@loevy.com

RE: FOIA Request 2020-2591for Coronavirus/COVID-19 records

Dear Mr. Topic:

Please find enclosed CDER's initial production of Coronavirus/COVID-19 records. This initial production comprises 52 pages of FDA internal reports on the use of chloroquine/hydroxychloroquine for the treatment of COVID-19. The pages are Bates numbered FDACDER000001 – FDACDER000052.

This is the first in a series of rolling productions.

Sincerely,

Howard R. Philips

Howard Philips
Supervisory Regulatory Counsel
Division of Information Disclosure Policy
Center for Drug Evaluation and Research

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Enclosures

Emergency Use Authorization (EUA) for chloroquine phosphate, an unapproved product and hydroxychloroquine sulfate, an unapproved use of an approved product
Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	EUA-039
Sponsor (entity requesting EUA or pre-EUA consideration)	Biomedical Advanced Research Authority (BARDA)
Manufacturer, if different from Sponsor	Bayer Pharmaceuticals Sandoz/Novartis
Submission Date(s)	March 26, 2020
Receipt Date(s)	March 26,2020
OND Division / Office	DAV
Reviewer Name(s)/Discipline(s)	Aimee Hodowanec, MD/Clinical Reviewer, Divison of Antivirals Mary Singer, MD, PhD/Medical Team Leader, Division of Antivirals Debra Birnkrant, MD/Director, Division of Antivirals John Farley, MD, MPH/Director (Acting), Office of Infectious Diseases Don Ashley, Director, Office of Compliance Linda Buhse, Office Director, Office of Surveillance, Office of Pharmaceutical Quality
Integrated Review Completion Date	March 28,2020
Proprietary Name)	Plaquenil Resochin
Established Name/Other names used during development	Chloroquine phosphate Hydroxychloroquine sulfate
Dosage Forms/Strengths	Chloroquine phosphate 250 mg Hydroxychloroquine sulfate 200 mg
Therapeutic Class	Antimalarial
Intended Use or Need for EUA	Treatment of COVID-19
Intended Population(s)	Treatment of: Adults and adolescents who weigh $\geq$50 kg and are hospitalized with COVID-19 when participation in a clinical trial is not available or feasible
Product in the Strategic National Stockpile (SNS)	Yes
Distributor, if other than Sponsor	NA

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I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2009-nCoV). The virus is now named SARS- CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

FDA has completed the review of the EUA-039. No further information is requested at this time.

Recommend EUA Issuance
The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

A. EUA Communications

The EUA will be issued for to treatment of:

- Adults and adolescents who weigh $\geq$ 50 kg and are hospitalized with COVID-19 when a clinical trial is not available, or participation is not feasible. Because data are needed on the effectiveness of these chloroquine phosphate and hydroxychloroquine sulfate products in this setting, preference will be given to use of these drugs for clinical trials.

B. Eligibility of the Product for an EUA

- This is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.
- Based on the scientific evidence available to FDA, it is reasonable to believe that these products may be effective in treating the serious or life-threatening disease, COVID-19. Based on the scientific evidence available to FDA, it is reasonable to believe that the potential benefits outweigh the known and potential risks of the product when used to treat adults and adolescents who weigh $\geq$50 kg and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible. There are no adequate, approved,

and available alternatives to the candidate products for treating, this serious or life-threatening disease.[2]

III. Proposed Use and Dosing of the Product Under the EUA

- Proposed use(s) under EUA –treatment of adults and adolescents who weigh ≥ 50 kg and are hospitalized with COVID-19 for whom participation in a clinical trial is not available or feasible
- Proposed dosing regimen(s) for use under EUA:

Chloroquine phosphate

- Adult and adolescent hospitalized patients weighing more than 50 kg: 1g orally once on day one followed by 500 mg orally once a day for four to seven days of total treatment based on clinical evaluation
- Recommended Laboratory and Electrocardiographic Monitoring: A baseline electrocardiogram should be obtained to assess for QT interval prolongation and other abnormalities. Baseline evaluation of renal and hepatic function is recommended.
- Pregnant or lactating patients: no change in dosing is recommended
- Use with caution in patients with renal[3] or hepatic impairment
- Rationale for dosing regimen: The optimal dose and duration of treatment is unknown. This dosing regimen is similar to what is being studied in clinical trials, is predicted to provide tissue concentrations in the lung that exceed the EC_{50} and does not significantly exceed the total exposure for which a safety profile has been established.

Hydroxychloroquine sulfate

- Adult and adolescents patients weighing more than 50 kg hospitalized with COVID-19: 800 mg orally once on day one followed by 400 mg orally once a day for four to seven days of total treatment based on clinical evaluation.
- Recommended Laboratory and Electrocardiographic Monitoring: A baseline electrocardiogram should be obtained to assess for QT interval prolongation and other abnormalities. Baseline evaluation of renal and hepatic function is recommended.
- Pregnant or lactating patients: no change in dosing is recommended
- Use with caution in patients with renal[3] or hepatic impairment
- Rationale for dosing regimen: The optimal dose and duration of treatment is unknown. This dosing regimen is similar to what is being studied in clinical trials, is predicted to provide tissue concentrations in the lung that exceed the

[2] Adequate/available status of approved products could be affected by, e.g., supply issues, allergies, suitability for specific populations.

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

EC_{50},[4] and does not significantly exceed the total exposure for which a safety profile has been established.

IV. Product Information (Dose Preparation and Administration)

- **Chloroquine phosphate** -
  - Preparation of adult dose – 250 mg tablets
  - Preparation of adolescent dose – 250 mg tablets
- Storage conditions below 30 degree Celsius
- Blister pack – may be supplied in 10 tablets per pack and up to five single blister packs within a carton
- Instructions for administration – per Healthcare Provider FACT Sheet
- Instructions for handling, if applicable NA

- **Hydroxychloroquine sulfate-**
  - Preparation of adult dose-200 mg tablets
  - Preparation of adolescent dose- 200 mg tablets
  - Storage - Store at 20° to 25°C (68° to 77°F)
  - Instructions for administration-per Healthcare Provider FACT Sheet
  - Instructions for handling, if applicable: NA

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Globally, according to the World Health Organization (WHO), approximately 509,164 confirmed cases of coronavirus disease 2019 (COVID-19) caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of March 27, 2020, including an estimated 23,335 deaths. In the US approximately, according to the Centers for Disease Control and Prevention (CDC), 85,356 cases of COVID-19 have been reported with 1246 deaths as of March 27, 2020. On March 11, 2020, the WHO declared the COVID-19 outbreak a pandemic.

Per the CDC (MMWR March 27, 2020 / 69(12);343-346), between February 12 and March 16, 2020, 4,226 COVID-19 cases were reported in the United States; 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths occurred among adults aged ≥65 years, with the highest percentage of severe outcomes among persons aged ≥85 years. These findings are similar to data from China, which indicated >80% of deaths occurred among persons aged ≥60 years (3). These preliminary data also demonstrate that severe illness leading to hospitalization, including ICU admission and death, can occur in adults of any age with COVID-19. In contrast, persons aged ≤19 years appear to have milder COVID-19 illness, with almost no hospitalizations or deaths reported to date in the United States in this age group.

There are currently no treatments approved by the FDA for treatment of COVID-19.

[4] Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020; doi: 10.1093/cid/ciaa237. [Epub ahead of print]

VI. Related Regulatory Submission(s)

Hydroxychloroquine and chloroquine are currently being evaluated for the prevention and treatment of COVID-19 under multiple INDs.

VII. Summary of Clinical Data

Several arguments have been made to suggest a potential for benefit of chloroquine and hydroxychloroquine in treating COVID-19. Clinical trials to assess this possibility of benefit are urgently needed and some are in process. The clinical community has shown substantial interest in potential uses of these drugs in this public health emergency. Because of the limitations and inconsistencies of the available data, continuation and expansion of assessment in well-designed clinical trials is considered to be highly important, at the same time that emergency uses of these products in carefully selected crisis settings might be considered.

At least 16 studies in multiple countries are listed on ClinicalTrials.gov for use of chloroquine or hydroxychloroquine to prevent or treat COVID-19. Additional trials are listed on the China clinical trials registry. Chinese media reports and articles based on such statements to the press[5] have stated that experts had treated over 100 COVID-19 patients with chloroquine and seen improvement in parameters such as "abatement of fever, improvement of CT images of lungs, the percentage of patients who became negative in viral nucleic acid tests and the time they need to do so." More complete publications are needed for additional information, such as details of selection of patients for treatment, and identification and comparability of control groups. One small randomized trial (NCT04261517) has been published in abstract form: although this NCT number is referred to in a commentary as showing positive preliminary outcomes,[6] the abstract itself (Chen et al.) reports very similar outcomes in patients randomized to hydroxychloroquine or control (although one hydroxychloroquine patient "transitioned to severe" from the "common COVID-19" status at entry) and the authors conclude the overall prognosis is good in "common COVID-19" and larger sample size would be needed to assess hydroxychloroquine effects.[7]

A group of French researchers has published a report of preliminary findings (day 6 results) from administration of hydroxychloroquine (with azithromycin added in some instances) to a group of patients at a center in Marseille, compared to a control group who either were treated at other hospitals or refused the treatment or had exclusion criteria for the study. Of 26 treated patients, 6 were designated as lost to follow-up ("dropout") because of early treatment cessation for reasons including transfer to ICU, death, leaving the hospital, or stopping treatment due to side effects; of the remaining 20, negative PCR of nasal swab on day 6 was reported in 70%, compared with 12.5% of the control group. Six of the treated patients had azithromycin added to their regimen to prevent bacterial superinfection with daily electrocardiographic monitoring; all 6 were

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[5] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020. DOI: 10.5582/bst.2020.01047. [Epub ahead of print]

[6] Mitja O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Glob Health. 2020. DOI:https://doi.org/10.1016/S2214-109X(20)30114-5. [Epub ahead of print]

[7] Chen J, Liu D, Liu Li L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-10 (COVID-19). J Zhenjiang Univ. 2020; DOI: 10.3785/j.issn.1008-9292.2020.03.03.

reported as virologically cured at day 6 (though one was noted as testing low positive again at day 8).[8] Although questions might be raised about the composition and comparability of the different groups in this study, the publication has raised high levels of interest in potential uses of hydroxychloroquine or chloroquine and the potential for combination with azithromycin.

A number of national guidelines have been reported as incorporating recommendations regarding use of chloroquine or hydroxychloroquine in the setting of COVID-19, including guidelines used in China and Korea. Expert assessments associated with a number of US medical institutions also include discussion of these drugs: for example, the March 23, 2020, update of the Johns Hopkins Abx Guide notes "Chinese Guidelines for COVID-19 suggest using chloroquine, traditional Chinese medicines, and an anti-IL6R drug, tocilizumab, as an anti-inflammatory agent in patients with extensive lung disease/severe illness and elevated IL-6 levels. These recommendations are not yet supported by robust clinical evidence" and in general advise "If a clinical trial available, consider enrolling patients rather than prescribing off-label drug use to assist in understanding whether intervention is efficacious for COVID-19."[9] The number of trials listed on ClinicalTrials.gov for chloroquine or hydroxychloroquine interventions against COVID-19 has been increasing, another indication of the interest in these drugs in this setting. Although continuation and expansion of well-designed clinical trials is clearly important, clinicians may perceive a need for these drugs in settings where clinical trials are not available or not feasible.

IX. Human Clinical Safety

Approved Labeling
As these are approved products there is considerable premarket and clinical safety data for the doses suggested for the FDA approved indications, but not for COVID-19.

Contraindications

Chloroquine phosphate 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 Chloroquine phosphate.

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.

Chloroquine (Aralen 2018)

- ✓ Retinal and visual field changes
- ✓ Hypersensitivity to 4-aminoquinolines

[8] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print]

[9]https://www hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_?q=covid-19

Hydroxychloroquine (Plaquenil 2019)

- ✓ Hypersensitivity to 4-aminoquinolines

Warnings and Precautions

Chloroquine (Aralen 2018)

- ✓ 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. Myocarditis/pericarditis, and cardiomyopathy may increase risk of arrythmia.
- ✓ Severe hypoglycemia including loss of consciousness that could be life threatening in patients with or without antidiabetic medications
- ✓ Hepatic Impairment, alcoholism, and use with other hepatotoxic drugs
- ✓ Hemolysis in G6PD deficient patients
- ✓ Irreversible retinal damage (risk factors: doses > 2.3 mg/kg for ≥ 5years, renal impairment, tamoxifen use, macular disease)
- ✓ Acute extrapyramidal disorders
- ✓ Muscular weakness with long-term therapy
- ✓ Worsening psoriasis and porphyria (precipitation of severe attacks)
- ✓ Potential Carcinogenic Risk (experimental animal data)
- ✓ Use in Pregnancy: Animal data show embryo-fetal development toxicity at 3-16 times the maximum recommended human therapeutic dose. Clinical data show no increase in birth defects or spontaneous abortions
- ✓ Hearing loss

Hydroxychloroquine (Plaquenil 2019)

- ✓ Cardiac Effects: cardiomyopathy (atrioventricular block, pulmonary hypertension, sick sinus syndrome or biventricular hypertrophy) and QT prolongation with acute and chronic use. Myocarditis/pericarditis, and cardiomyopathy may increase risk of arrythmia.
- ✓ Severe hypoglycemia including loss of consciousness that could be life threatening in patients with or without antidiabetic medications
- ✓ Hepatic impairment, alcoholism, use with concomitant hepatotoxic drugs: may need dose reduction
- ✓ Renal Impairment: may need dose reduction
- ✓ Hematologic effects: aplastic anemia, agranulocytosis, thrombocytopenia; hemolysis in G6PD deficient patients
- ✓ Seizures: may lower seizure threshold
- ✓ Irreversible retinal damage (doses > 6.5 mg/kg for ≥ 5years, renal impairment, tamoxifen use, macular disease)
- ✓ Proximal myopathy and neuropathy (skeletal muscle myopathy or neuropathy leading to progressive weakness and atrophy of proximal muscle groups, depressed tendon reflexes, and abnormal nerve conduction)
- ✓ Neuropsychiatric events, including suicidality
- ✓ Worsening psoriasis and porphyria (precipitation of severe attacks)
- ✓

- ✓ Dermatitis

Drug-Drug Interactions

Chloroquine (Aralen 2018)

- ✓ Antacids: reduce chloroquine (CQ) absorption
- ✓ Cimetidine: increase CQ plasma levels
- ✓ Insulin and other antidiabetic drugs: risk of hypoglycemia. Need to decrease dose of antidiabetic drugs.
- ✓ Arrhythmogenic drugs, e.g. moxifloxacin, azithromycin and amiodarone: risk of ventricular arrhythmias.
- ✓ Ampicillin: CQ reduces ampicillin bioavailability
- ✓ Cyclosporine: increase in cyclosporin levels
- ✓ Mefloquine: increased seizure risk
- ✓ Rabies vaccine: CQ reduces immunogenicity to vaccine
- ✓ Praziquantel: CQ reduces praziquantel bioavailability
- ✓ Tamoxifen: increased retinal toxicity

Hydroxychloroquine (Plaquenil 2019)

- ✓ Digoxin: Hydroxychloroquine (HCQ) increases digoxin levels
- ✓ Insulin and other antidiabetic drugs: risk of hypoglycemia. May need to decrease dose of antidiabetic drugs
- ✓ Arrhythmogenic drugs, e.g. moxifloxacin, azithromycin, and amiodarone: risk of ventricular arrhythmias
- ✓ Mefloquine and other drugs that lower seizure threshold: increased seizure risk
- ✓ Antiepileptics: HCQ may lower efficacy
- ✓ Methotrexate: may increase risk of adverse reactions with methotrexate
- ✓ Cyclosporine: increase in cyclosporin levels
- ✓ Antacids: reduce CQ absorption, may affect HCQ
- ✓ Cimetidine: increase CQ plasma levels, may affect HCQ
- ✓ Praziquantel: CQ (HCQ) reduces praziquantel bioavailability

Overdosage

- **Chloroquine (Aralen 2018) and Hydroxychloroquine (Plaquenil 2019)**
  Chloroquine is very rapidly and completely absorbed after ingestion. Toxic doses of chloroquine can be fatal. As little as 1 g of chloroquine or hydroxychloroquine may be fatal in children. Toxic symptoms can occur within minutes. The symptoms of overdosage may include nausea, vomiting, headache, drowsiness, visual disturbances, cardiovascular collapse, convulsions, hypokalemia, rhythm and conduction disorders including QT prolongation, torsades de pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden, potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose. Cases of extrapyramidal disorders have also been reported in the context of chloroquine overdose.

  Chloroquine overdose is a life-threatening emergency and should be managed with cardio-respiratory and hemodynamic support, monitoring of potassium along with management of arrhythmias and convulsions, as necessary. A patient who survives the acute phase and is asymptomatic should be closely observed until all clinical features of toxicity resolve.

Published Literature

Chloroquine, a 4-aminoquinoline, has been in use as an antimalarial drug, for both treatment and for chemoprophylaxis of malaria since 1949. It has activity against the blood stages of *Plasmodium ovale, P. malariae,* and susceptible strains of *P. vivax* and P. *falciparum.* Chloroquine may also be used for treatment of connective tissue diseases but is largely replaced by hydroxychloroquine in the US. Hydroxychloroquine, a derivative of chloroquine, has been in use since 1955 and is used for the treatment and prevention of malaria as well as for rheumatoid arthritis and lupus erythematosus.

Chloroquine phosphate is generally well-tolerated when taken at the recommended oral doses for treatment or prophylaxis of malaria. Side effects reported in travelers taking chloroquine for prophylaxis of malaria include gastrointestinal upset, headache, dizziness, blurred vision, insomnia, and pruritus, and exacerbation of psoriasis.[10] Chloroquine-induced itching is common among African descent or African descent with dark skin, but much less common in other races.

[10] Steinhardt LC, Magill AJ, Arguin PM. Review: Malaria chemoprophylaxis for travelers to Latin America. Am J Trop Med Hyg. 2011 Dec;85(6):1015-24. doi:10.4269/ajtmh.2011.11-0464.

Photosensitivity [11] and other less common skin adverse effects such as rash, pleomorphic skin eruptions, lichen planus-like eruptions, urticaria and skin pigmentation changes may occur.[12,13]

The most severe side effects occur with prolonged use, for example, neuromyopathy with long-term malaria prophylaxis and retinopathy with high cumulative doses used for treatment of connective tissue diseases.[14,15] Retinal toxicity is associated with long term use of chloroquine and hydroxychloroquine; however, it is rarely seen with chloroquine in the United States as hydroxychloroquine is the aminoquinoline of choice for treatment of connective tissue diseases. The risk of retinal toxicity is dependent on daily dose by weight and duration of use. At recommended doses the risk of retinal toxicity with up to five years of use is under 1%. Annual ophthalmology screening is recommended starting after five years of use (earlier if risk factors for retinopathy are present).[16]

Chloroquine- or hydroxychloroquine-related cardiac conduction disorders (i.e. QT prolongation, ventricular arrhythmias) are rare but life-threatening adverse reactions and are usually associated with long-term use and high cumulative doses.[17]

Chloroquine is a rare cause of clinically apparent acute liver injury.[18]

A variety of neuropsychiatric adverse events have been reported with chloroquine (and hydroxychloroquine), from mild emotional lability to anxiety, agitation, and rare cases of psychosis. Seizures, syndromes of involuntary movements, suicidal behavior and ototoxicity have also been reported occasionally.[14] Case reports of overdoses of chloroquine phosphate leading to

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[11] van Weelden H, Bolling HH, Baart de la Faille H, van der Leun JC. Photosensitivity caused by chloroquine. Arch Dermatol. 1982;118:290

[12] Janier M, Froidevaux D, Lons-Danic D, Daniel F. Acute generalized exanthematous pustulosis due to the combination of chloroquine and proguanil. Dermatology. 1998;196:271

[13] Pragya Ashok Nair and Trusha Patel. Palmoplantar exfoliation due to chloroquine. Indian J Pharmacol. 2017 Mar-Apr; 49(2): 205–207

[14] Wittes R. Adverse reactions to chloroquine and amodiaquine as used for malaria prophylaxis: a review of the literature. Can Fam Physician 1987; 33:2644-9.

[15] Stein M, Bell MJ, Ang LC. Hydroxychloroquine neuromyotoxicity. J Rheumatol 2000;27(12):2927-31.

[16] Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016 Jun;123(6):1386-94. doi: 10.1016/j.ophtha.2016.01.058.

[17] Chatre C., Roubille F, Vernhet H, et al. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. Drug Saf (2018) 41:919–931

[18] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-2017 Feb 2.

death, cardiac arrest, and neurotoxic vestibulopathy have been reported.[19,20,21] Rare cases of idiosyncratic reactions, such as erythema multiforme and bone marrow toxicity, have occurred.[22]

Chloroquine and hydroxychloroquine are generally considered safe in pregnancy. The available clinical data support the compatibility of chloroquine treatment in pregnancy and breastfeeding.[23,24,25,26,27,28] In a cohort of US government employees taking weekly chloroquine as prophylaxis throughout pregnancy in 1969–1978, the prevalence of newborns with congenital abnormality was not different from that of those who were not exposed to chloroquine. [29]

Postmarketing Safety Review Findings

A high-level review of postmarketing reports for chloroquine and hydroxychloroquine has been performed in FAERS for 2010-2020. The overall safety profile for both chloroquine and hydroxychloroquine was consistent with approved product labeling for Aralen and Plaquenil. Generally, for hydroxychloroquine the identified unlabeled adverse events reflected the condition under treatment. For chloroquine, unlabeled adverse events of clinical interest included suicidal ideation, toxic encephalopathy, and acute kidney injury.

Recommendations for Information to Include in Health Care Provider Fact Sheets

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[19] Drasch G, Eisenmenger W. Death following administration of 1,250 mg chloroquine in porphyria cutanea tarda. Z Rechtsmed. 1986;97(4):285-93

[20] Bethlehem C, Jongsma M, Korporaal-Heijman J, et al. Cardiac arrest following chloroquine overdose treated with bicarbonate and lipid emulsion. Neth J Med. 2019 Jun;77(5):186-188. PubMed PMID: 31264584.

[21] Chansky PB, Werth VP. Accidental hydroxychloroquine overdose resulting in neurotoxic vestibulopathy. BMJ Case Rep. 2017 Apr 12;2017.

[22] Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf. 2004;27(1):25

[23] Law I, Ilett KF, Hackett LP, et al. Transfer of chloroquine and desethylchloroquine across the placenta and into milk in Melanesian mothers. Br J Clin Pharmacol. 2008;65(5):674–679

[24] Divala TH, Mungwira RG, Mawindo PM, wt al. Chloroquine as weekly chemoprophylaxis or intermittent treatment to prevent malaria in pregnancy in Malawi: a randomised controlled trial. Lancet Infect Dis. 2018;18(10):1097-1107. doi: 10.1016/S1473-3099(18)30415-8.

[25] Lowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum. 2006 Nov;54(11):3640-7. PubMed PMID: 17075810.

[26] McGready Makoto Saito, Mary Ellen Gilder, Rose McGready et al. Antimalarial drugs for treating and preventing malaria in pregnant and lactating women. Expert Opinion on Drug Safety 2018;17:11:1129-1144. DOI: 10.1080/14740338.2018.1535593

[27] McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. Trans R Soc Trop Med Hyg. 2002;96(2):180–184.

[28] Kaplan YC, Ozsarfati J, Nickel C, and Koren G. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: A systemic review and meta-analysis. Br J Clin Pharmacol. 2016;81(5)835-848.

[29] Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. Br Med J Clin Res. 1985;290(6480):1466–1467.

Based on a review of labeling for approved products, postmarketing safety, published literature, and consideration of the use of chloroquine phosphate and hydroxychloroquine sulfate from the Strategic National Stockpile under the EUA 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, the following information is recommended for inclusion in the Health Care Provider Fact Sheets:

Contraindications
DRUG is contraindicated in the presence of retinal or visual field changes of any etiology and in patients with known hypersensitivity to 4-aminoquinoline compounds. DRUG 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 DRUG.

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.

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

Severe hypoglycemia: DRUG 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 DRUG is known to concentrate in the liver, it should be used with caution in patients with hepatitis, other hepatic disease, alcoholism or in conjunction with known hepatotoxic drugs.

Renal impairment: DRUG 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.[30]

[30] 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.

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

Worsening of psoriasis and porphyria: Use of DRUG in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria, the condition may be exacerbated. DRUG 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 DRUG.

Drug Interactions

Digoxin: Concomitant DRUG and digoxin therapy may result in increased serum digoxin levels. Serum digoxin levels should be closely monitored in patients receiving both drugs.

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

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

Insulin and other antidiabetic drugs: As DRUG 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 DRUG is used concomitantly with other arrhythmogenic drugs, such as amiodarone, azithromycin or moxifloxacin.

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

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

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

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

Tamoxifen: Concomitant use of DRUG 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 DRUG.

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 DRUG 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 DRUG in pregnant women.

X. Specific Populations

- Dosing adjustments may be needed for patients with severe renal disease.
- Use in Pregnancy:
  - **Chloroquine (Aralen 2018)**
    Animal data show embryo-fetal development toxicity at 3-16 times the maximum recommended human therapeutic dose. Clinical data at approved doses for treatment and prophylaxis of malaria show no increase in birth defects or spontaneous abortions. Recommend that providers review benefits and risks before prescribing.
  - **Hydroxychloroquine (Plaquenil 2019)**
    Animal data show embryonic deaths and malformations of anophthalmia and microphthalmia in the offspring when pregnant rats received large doses of chloroquine. Clinical data show no increase in the rate of birth defects. Recommend that providers review benefits and risks before prescribing.

- Geriatric Use
  - **Chloroquine (Aralen 2018) and Hydroxychloroquine (Plaquenil 2019)**
    Insufficient numbers of subjects aged 65 years and older were included in clinical trials. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater. Monitor renal function.

XI. Human Clinical Pharmacology

Chloroquine (Aralen 2018)

- Rapidly and almost completely absorbed
- 55% of the drug is protein bound
- Large distribution to various tissues
- Main metabolite: desethylchloroquine (accounts for ¼ of total drug in urine)
- Unchanged chloroquine accounts for > 50% of total drug in urine

Hydroxychloroquine (Plaquenil 2019)

- Following single 200 mg oral dose:
  - blood
    - T_{max}: 3.3 hours
    - Mean C_{max}: 129.6 ng/mL
    - Half-life ($T_{1/2}$): 22.4 days
  - Plasma
    - T_{max}: 3.7 hours
    - Mean C_{max}: 50.3 ng/mL
    - $T_{1/2}$: 123.5 days
- Following chronic oral administration:
  - Terminal $T_{1/2}$: 40 to 50 days
  - Long $T_{1/2}$ is due to extensive tissue uptake
  - Major metabolite: desethylhydroxychloroquine (DHCQ)
- Renal clearance of unchanged drug: 16 to 30 % and not correlated with CrCL

XIII. Nonclinical Data to Support Efficacy

Antiviral activity of chloroquine and hydroxychloroquine against the COVID-19 virus (SARS-CoV-2) has been reported in cell culture studies.

Researchers have reported that chloroquine blocked entry of a clinically derived strain of SARS-CoV-2 (nCoV-2019BetaCoV/Wuhan/WIV04/2019) into Vero cells preincubated with the drug, with a half-maximal effective concentration (EC_{50}) of 1.13 micromolar and selectivity index (50% cytotoxic concentration(CC_{50})/EC_{50}) of 88.5.[31] Another publication from the same group reported that hydroxychloroquine was also active though slightly less so (and chloroquine showed somewhat higher EC_{50} than in the previous publication, attributed to passaging of the viral

[31] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-71.

strain).[32] In a manuscript in press, Yao et al. reported an EC_{50} at 48 hours of 5.47 micromolar for chloroquine and 0.72 micromolar for hydroxychloroquine when drugs were added 2 hours after infection of Vero cells with SARS-CoV-2 (C-Tan-nCoV Wuhan strain 01).[33] Both research groups noted that chloroquine has been reported to have activity against a variety of viruses in cell culture, and is presumed to act by modulating pH to inhibit membrane fusion (interfering with endosomal acidification) as well as several potential other mechanisms. Other authors have also noted the history of activity against many viruses in vitro while suggesting that such in vitro findings have not been associated with equally impressive in vivo findings (for example, chloroquine not found to prevent influenza or provide clinical benefit in dengue; and in chikungunya infection, chloroquine was reported to show antiviral activity in vitro but to worsen outcomes in animal models and to be associated with increased chronic arthralgia in humans).[34,35]

XIV. Supply Information

- Chloroquine Phosphate One Course –ten to eighteen 250 milligram tablets
- Hydroxychloroquine sulfate - One Course ten to eighteen 200 milligram tablets

- Number of treatment courses

  Chloroquine Phosphate - expected # of treatment courses based on maximum treatment length - 56,000

  Hydroxychloroquine sulfate expected # of treatment courses based on maximum treatment length 7.2 million

Chloroquine Phosphate

The product is not approved in the US and is currently being supplied in blister packs containing ten 250 milligram tablets. The blister packs are in a carton. The carton contains prescribing information that is not the US approved labeling for this product. The following issues were identified in the review of the product

Container Label

[32] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative o chloroquine, is effective in inhibiting SARS-CoV02 infection in vitro. Cell Discov 2020; doi: 10.1038/s41421-020-0156-0. [epub ahead of print]

[33] Yao X, Ye F, Zhang M, et al. In vitro activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020; doi: 10.1093/cid/ciaa237. [Epub ahead of print]

[34] Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Research 2020; doi: 10.1016/j.antiviral.2020.104762. [Epub ahead of print]

[35] Roques P, Thiberville SD, Dupuis-Maguiraga L, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. Viruses 2018; 10(5). pii: E268.

1. The labeling states this product contains the same active ingredient and amounts of chloroquine phosphate as the U.S. approved 250 mg Chloroquine Phosphate Tablets.
2. There is the risk of end-users not being able to identify the drug when they separate the tablets from the pack when dispensing. Each tablet is not in a perforated unit-dose packaging containing all of the important information over each blister cell so that the important information remains available to the end-user up to the point at which the last tablet is removed. Additionally, it doesn't appear to be any imprint code on the tablets or mention of it in the PI.

   Since dispensing is in the setting of a hospital or clinical trial, such pharmacies have experience in repackaging drugs for in-patient dispensing and operating procedures to minimize medication errors. Nonetheless, to reduce any potential errors, the Prescriber FACT sheet contains the following statement. - *If the drug is dispensed separate from the blister pack for inpatient use, the dispensing container should clearly identify the drug and dosage strength.*
3. There is potential for end-users to misinterpret the manufacture date (JAN 2020) as the expiration date (EXP DEC 2022) if tablets are pushed through at the location of the expiration date.
4. While stored in the hospital pharmacy, both issues #1 and #2 may be mitigated by the fact that the product is supposed to be stored in the carton to protect from light ("Store protected from light"). The carton labeling provides adequate labeling with the drug product name and the expiration date. However, when the pharmacy staff separates 2 tablets for the COVID-19 dose of 500 mg to send to the patient floor, the tablets will not be in the carton. The lack of unit-dose perforated packaging with the important information on each unit-dose such as drug name and expiration date will lead to HCPs being unable to identify the product. As stated above since dispensing is in the setting of a hospital or clinical trial, such pharmacies have experience in repackaging drugs for in-patient dispensing and operating procedures to minimize medication errors. Nonetheless, to reduce any potential errors, the Prescriber FACT sheet contains the following statement. - *If the drug is dispensed separate from the blister pack for inpatient use, the dispensing container should clearly identify the drug and dosage strength.*

Carton Labeling

The carton labeling lists both the expiration date and the manufactured date. Drug products in the US typically provide the expiration date only. However, because the carton labeling lists the expiration date directly below the manufactured date, end-users will likely interpret this expiration date correctly.

Prescribing Information (PI)

There are additional indications in the product PI that are not listed in the approved U.S. labeling. However, this appears appropriate considering the product is being used

on EUA. OND has determined that this is acceptable and will not lead to an increased risk given the use under the EUA and the Healthcare Provider FACT sheet.

XV. Chemistry, Manufacturing, and Controls Information

- A sample of the chloroquine phosphate has been tested for consistency with USP standards as this is an unapproved drug manufactured outside of the US
- There are no quality concerns with hydroxychloroquine sulfate.

XVI. Manufacturing Site Inspections

Bayer's One Million Tablet Donation of Chloroquine Manufactured in India

1. API Facility
   IPCA Laboratories Limited
   89A-B/90/91
   Industrial Estate
   PoloGround, Indore-452003
   India

2. Finished Drug Product Facility
   IPCA Laboratories LTD (Unit-I)
   C-6, Sara industrial Estate
   Chakrata Road
   Rampur, Dehradun
   248197, Uttarakhand, India

- Bayer donated 1 million tablets of chloroquine manufactured by never previously inspected ICPA facilities in India. This material is the only known large scale commercial source of chloroquine identified by CDER that could possibly be available for use this week. ICPA has a low reputation for quality. All known ICPA facilities previously inspected by FDA are OAI and on import alert. The API and FDF facilities used to manufacture this chloroquine are presumed to have even lower standards of quality. Given the lack of an approved application and any inspection history, OTR and USP are conducting tests on the donated chloroquine to help determine its level of quality. In addition, facility and manufacturing information provided by Bayer is being reviewed. The product will be available under this EUA if it passes critical testing requirements.

As explained above, the chloroquine tablets donation from Bayer was manufactured at IPCA facilities in India, which have never been inspected by the FDA and are not included in any approved application. Thus, we have little to no information regarding CGMP compliance at these facilities. Accordingly, the Office of Compliance recommends a waiver pursuant to [21 USC § 360bbb-3(e)(3)].[1]

The Office of Compliance issued an enforcement discretion to allow the Bayer chloroquine to be imported into the U.S. on the condition that it be tested by OTR and USP and meets established specifications, prior to any use of the product. All specifications for identification, assay, organic impurities, dissolution, and residual solvents were met for chloroquine phosphate tablets. Results indicate tablets meet USP compendial standards

Sandoz/Novartis Donation of Hydroxychloroquine

1. API Facility
   (b) (4)
   [redacted]

2. Finished Drug Product Facility:
   FEI: 3000210731
   Eon Labs Inc. / Sandoz Inc.
   4700 Sandoz Drive
   Wilson, NC, USA
   Last inspection: 1/25/2019, NAI

Sandoz/Novartis has offered to donate the following amounts of hydroxychloroquine to the SNS:

130 million tablets of hydroxychloroquine:
- 30 million immediately
- 30 million by April 30th
- 25 million by May 30th
- 45 million TBD

Sandoz manufactures the FDF hydroxychloroquine to be donated to the U.S.G at its Wilson, NC site. There are no known CGMP or quality issues concerning the Wilson, NC site.

Sandoz is using API supplied by (b) (4) in (b) (4) to produce the hydroxychloroquine to be donated to the USG. There are no known CGMP or quality issues with this source of API. However, (b) (4) [redacted]

XVII. Clinical Trial Site Inspections

NA

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

The COVID-19 pandemic continues to grow with more than 100,000 confirmed cases and over 1,500 deaths in the U.S. at this time based on the Johns Hopkins Operations dashboard. New York City has been particularly heavily impacted by COVID-19, with reports of health care systems being near or above capacity. Elderly patients and those with comorbidities appear to be most susceptible to the more severe and sometimes fatal COVID-19 presentations. Presently, there are no approved therapies for the treatment of COVID-19. Given the lack of available therapies, there has been a great interest in identifying potential existing drugs that could be repurposed for COVID-19 use.

Chloroquine and hydroxychloroquine are antimalarial drugs that have been shown to have in vitro activity against SARS-CoV-2 at drug concentrations achievable by doses considered safe in humans.[36,37,38] Notably, chloroquine has been found to have in vitro activity against numerous viruses, but historically in vivo findings have been less promising. Further, some have raised concerns that the immune modulating effects of chloroquine and hydroxychloroquine could prove to be detrimental in patients with COVID-19.[39] Nonetheless, these in vitro findings have led clinicians across the world to consider their potential utility in patients with COVID-19. Numerous clinical trials to study chloroquine and hydroxychloroquine for treatment and prevention of COVID-19 have been initiated or are planned. Minimal data are available to date, though a brief report from a Chinese study of 100 COVID-19 patients reported clinical improvement with chloroquine or hydroxychloroquine treatment versus an unspecified control.[40] Additionally, in a recent survey by French researchers involving 20 COVID-19 patients, hydroxychloroquine alone and in combination with azithromycin was reported to be associated with viral load reduction over 6 days. The viral load changes were statistically significant compared to a nonrandomized control group and were more pronounced in patients who received the combination.[41]

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[36] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-71.

[37] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative o chloroquine, is effective in inhibiting SARS-CoV02 infection in vitro. Cell Discov 2020; doi: 10.1038/s41421-020-0156-0. [epub ahead of print]

[38] Yao X, Ye F, Zhang M, et al. In vitro activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020; doi: 10.1093/cid/ciaa237. [Epub ahead of print]

[39] Guastalegname M, Vallone A. Could chloroquine/hydroxychloroquine be harmful in coronavirus disease 2019 (COVID-19) treatment? Clin Infect Dis 2020; DOI: 10.1093/cid/ciaa321. [epub ahead of print]

[40] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020. DOI: 10.5582/bst.2020.01047. [Epub ahead of print]

[41] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print]

The safety profiles of chloroquine and hydroxychloroquine are well established as they are commonly used anti-malarial drugs and, in the case of hydroxychloroquine, used for rheumatoid arthritis and systemic lupus erythematosus as well. The recommended dosing for chloroquine and hydroxychloroquine under this EUA is generally within the range of that recommended in the approved labeling. In general, the drugs are well-tolerated, though adverse reactions can include QTc prolongation and ocular, neuropsychiatric, cardiac, and hematologic toxicity.

The effectiveness of chloroquine and hydroxychloroquine for the treatment of COVID-19 is not yet supported by robust clinical evidence. There is a clear need for continuation and expansion of well-designed clinical trials. However, in settings where clinical trials are not available or not feasible, access to these drugs may be of value in treating COVID-19. We recommend that access to these experimental drugs through EUA be limited to hospitalized patients for whom participation in a clinical trial is not available or feasible. Hospitalized patients have greater prospect of benefit (compared to ambulatory patients with mild illness) and can be more closely monitored for potential toxicity. Children have been shown to have mild disease for the most part and are not likely to derive significant benefit from hydroxychloroquine or chloroquine. Further, children and adolescents weighing less than 50 kg require weight-based dosing. Therefore, we conclude that in adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 and for whom participation in a clinical trial is not available or feasible, the potential benefits of chloroquine and hydroxychloroquine outweigh the known and potential risks.

XXI. Considerations for Adverse Event (AE) Monitoring and Reporting

This product will either be used in clinical trials or in clinical practice. If used in clinical trials done under IND, FDA IND safety reporting regulations will apply. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

The prescribing health care provider and/or the provider's designee will be responsible for reporting medication errors and adverse events (death, serious adverse events*) occurring during Chloroquine phosphate or Hydroxychloroquine Sulfate treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "[Chloroquine phosphate] or [Hydroxychloroquine Sulfate] Treatment under Emergency Use Authorization (EUA).

- Adverse event reports will be submitted 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/UCM

163919.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 state "[**Chloroquine phosphate] or [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.

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

This language should be consistent with the Letter of Authorization. Include all:

- Mandatory Requirements (refer to EUA Guidance, Conditions of Authorization)

1. Adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 infection 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 chloroquine phosphate or 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 chloroquine phosphate or hydroxychloroquine sulfate, and
    c. Informed that:
        i. Chloroquine phosphate is an unapproved drug which is authorized for the unapproved use under this Emergency Use Authorization.
        ii. Hydroxychloroquine sulfate is an approved drug which 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 chloroquine phosphate or 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 chloroquine phosphate or hydroxychloroquine sulfate treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "**Chloroquine phosphate or hydroxychloroquine sulfate treatment under Emergency Use Authorization (EUA)."** in the description section of the report (see Section XXI above).

- 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
  - Complete and submit FDA Form 3500 (health professional) or FDA Form 3500B (consumer/patient) by fax (1-800-FDA-0178) (these forms can be found via link above) Call 1-800-FDA-1088 for questions
  - Submitted reports should state "Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "**Hydroxychloroquine Sulfate Treatment under EUA"**
  - **Chloroquine phosphate 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.

- Discretionary Requirements (refer to EUA Guidance, Conditions of Authorization)

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

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

- Chloroquine Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Chloroquine Fact Sheet for Patients and Parents/Caregivers (See Section XXVI. Appendices)

- Hydroxychloroquine Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Hydroxychloroquine Fact Sheet for Patients and Parents/Caregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps

- Rigorous, controlled, adequately powered clinical trials are needed to assess the safety and efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19.

- There has been an interest in studying the combination of hydroxychloroquine and azithromycin for the treatment of COVID-19. Given that both azithromycin and hydroxychloroquine are QT-prolonging agents, caution should be used when combining these drugs and close monitoring is recommended.

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Johns Hopkins Abx Guide. **Coronavirus COVID-19 (SARS-CoV-2)**
Paul G. Auwaerter, M.D.
Updated: March 23, 2020

XXVI. Appendices

1. Fact Sheets for Health Care Providers
2. Fact Sheets for Patients and Parent/Caregivers
3. Compendial Testing Chloroquine

John Farley -S

Digitally signed by John Farley -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John Farley -S, 0.9.2342.19200300.100.1.1=2000329366
Date: 2020.03.28 23:09:32 -04'00'

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN D WINESTOCK
03/29/2020 10:22:12 AM
Signatory for this review is John Farley.

ADDENDUM to Emergency Use Authorization EUA-039 for chloroquine phosphate, an unapproved product and hydroxychloroquine sulfate, an unapproved use of an approved product
Center for Drug Evaluation and Research (CDER) Review
April 10, 2020

Pursuant this EUA, BARDA has requested, and FDA has concurred, additional supply of unapproved chloroquine phosphate from Bayer. The Memo is being updated to reflect the donations from Bayer to date:

XVI. Manufacturing Site Inspections

Bayer's Two Million Tablet Donation of Chloroquine Phosphate Manufactured in Pakistan

1. API Facility
   IPCA Laboratories Limited
   89A-B/90/91
   Industrial Estate
   PoloGround, Indore-452003
   India

2. Finished Drug Product Facility
   Bayer Pakistan Private Limited
   C-21, S.I.T.E. Area, Karachi – 75700
   Karachi, Pakistan

Bayer donated 2 million tablets of chloroquine phosphate. This product was manufactured at facilities that have never been inspected by FDA. The API was manufactured at an IPCA facility in India, while the finished drug product was produced at a Bayer facility in Pakistan. IPCA's facilities have had various compliance actions taken against them. All known IPCA facilities previously inspected by FDA are OAI and on import alert. As FDA has limited information regarding the facility that manufactures the API, it is presumed that it may also have a similar or worse compliance profile. The agency does not have information from another regulatory agency regarding the CGMP status of the Bayer, Pakistan facility Given the lack of an approved application and any inspection history, FDA conducted tests on samples of the donated chloroquine phosphate tablets to help determine its level of quality. In addition, facility and

manufacturing information provided by Bayer and IPCA was reviewed. The product is available under this EUA since it passed compendial testing requirements.

The Office of Compliance exercised enforcement discretion to allow the Bayer chloroquine phosphate to be imported into the U.S. based on the condition that it would be tested by FDA and meet established specifications prior to any use of the product.

All samples met specifications for compendial testing including identity, assay, organic impurities, dissolution, residual solvents, and heavy metal analysis. Unknown impurities were identified as ester flavorants in the samples. The ester compounds were subsequently identified as being associated with fruit flavoring (banana), in quantities consistent with low level contamination. Additional screening of the tablets was conducted using LC-MS and no indication of any gross contamination was seen.

Based on this information, CDER does not have any information to indicate that the presence of these flavorants represents a significant risk at this time and clears distribution of the product from the SNS, consistent with the terms of the EUA. Bayer will be requested to investigate the occurrence of these flavorants in the product and to submit their findings to the Agency.

Accordingly, CDER recommends a waiver pursuant to [21 USC § 360bbb-3(e)(3)].[1]

ATTACHMENT

[1] 21 USC § 360bbb-3(e)(3): Good manufacturing practice--With respect to the emergency use of a product for which an authorization under this section is issued (whether an unapproved product or an unapproved use of an approved product), the Secretary may waive or limit, to the extent appropriate given the circumstances of the emergency, requirements regarding current good manufacturing practice otherwise applicable to the manufacture, processing, packing, or holding of products subject to regulation under this Act, including such requirements established under section 501.

John Farley -S

Digitally signed by John Farley -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John Farley -S, 0.9.2342.19200300.100.1.1=2000329366
Date: 2020.04.13 16:51:32 -04'00'

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN D WINESTOCK
04/18/2020 01:27:03 PM

ADDENDUM to Emergency Use Authorization EUA-039 for chloroquine phosphate, an unapproved product and hydroxychloroquine sulfate, an unapproved use of an approved product
Center for Drug Evaluation and Research (CDER) Review
April 3, 2020

Pursuant to Section IV. E of this EUA, BARDA has requested, and FDA has concurred, with the additional condition that the prescribing health care provider and/or the provider's designee are/is responsible for submitting patient outcomes reports as follows:

> Complete and submit the report online:
> **Mandatory Patient Outcome Reporting Survey - EUA for Chloroquine Phosphate and Hydroxychloroquine Sulfate** https://euachloroquine-hydroxychloroquine-outcome.ppdi.com/

This additional requirement is reflected in the amended health care provider fact sheets, attached to this addendum.

Attachment:

Revised FACT Sheets
Request from BARDA

John Farley -S

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FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF CHLOROQUINE PHOSPHATE 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 chloroquine phosphate 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 chloroquine phosphate 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.

Chloroquine phosphate 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, **ALL SERIOUS ADVERSE EVENTS**, and **CLINICAL OUTCOMES** related to chloroquine phosphate. See specific reporting instructions below.

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

The suggested dose under this EUA for chloroquine phosphate 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 1 gram of chloroquine phosphate on day one, followed by 500 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 chloroquine phosphate 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 chloroquine phosphate under the EUA. Indication for COVID-19 is not part of the FDA-approved labeling but chloroquine phosphate information for other FDA-approved indications, including pharmacokinetics and safety profile, may be found in an FDA-approved package insert for chloroquine phosphate at https://dailymed.nlm.nih.gov/dailymed/.

The chloroquine product from the SNS may contain a package insert that is not the FDA approved labeling. Please refer to this fact sheet for information on use of chloroquine phosphate under the EUA and the above link for FDA approved labeling for additional information.

Contraindications
Chloroquine phosphate is contraindicated in the presence of retinal or visual field changes of any etiology and in patients with known hypersensitivity to 4-aminoquinoline compounds. Chloroquine phosphate 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 Chloroquine phosphate.

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

The suggested dose under this EUA for chloroquine phosphate 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 1 gram of chloroquine phosphate on day one, followed by 500 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.

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[1] The dosage of chloroquine phosphate is often expressed in terms of equivalent chloroquine base. Each 250 milligram tablet of chloroquine phosphate is equivalent to 150 milligram base and each 500 milligram tablet of chloroquine phosphate is equivalent to 300 milligram base. The dosing suggested in the Fact Sheet is for chloroquine phosphate.

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

Severe hypoglycemia: Chloroquine phosphate 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 chloroquine phosphate is known to concentrate in the liver, it should be used with caution in patients with hepatitis, other hepatic disease, alcoholism or in conjunction with known hepatotoxic drugs.

Renal impairment: Chloroquine phosphate 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.[2]

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

Worsening of psoriasis and porphyria: Use of chloroquine phosphate in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria, the condition may be exacerbated. Chloroquine phosphate 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 chloroquine phosphate.

Drug Interactions

Digoxin: Concomitant chloroquine phosphate and digoxin therapy may result in increased serum digoxin levels. Serum digoxin levels should be closely monitored in patients receiving both drugs.

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

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

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

Insulin and other antidiabetic drugs: As chloroquine phosphate 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 chloroquine phosphate is used concomitantly with other arrhythmogenic drugs, such as amiodarone, azithromycin or moxifloxacin.

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

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

Mefloquine: Co-administration of chloroquine phosphate and mefloquine may increase the risk of convulsions.

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

Tamoxifen: Concomitant use of chloroquine phosphate 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 chloroquine phosphate.

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 chloroquine phosphate 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 chloroquine phosphate in pregnant women.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider administering chloroquine phosphate, you should, prior to prescribing/dispensing in accordance with applicable state and local law, provide your patients with the Fact Sheet for Patients and the pamphlet titled “Emergency Use Authorization (EUA) of Chloroquine Phosphate- 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 of chloroquine phosphate, some of which is supplied in packages containing blister packs of 10

pills with prescribing information that is not FDA-approved labeling for chloroquine phosphate
2. That the patient has the option to accept or refuse administration of chloroquine phosphate
3. The potential consequences of refusing chloroquine phosphate
4. The significant known and potential risks and benefits of chloroquine phosphate, 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 chloroquine phosphate to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after chloroquine phosphate is administered.

If the drug is dispensed separate from the blister pack for inpatient use, the dispensing container should clearly identify the drug and dosage strength.

MANDATORY REQUIREMENTS FOR CHLOROQUINE PHOSPHATE ADMINISTRATION UNDER EUA

In order to mitigate the risks of using this product for an unapproved use under EUA and to optimize the potential benefit of chloroquine phosphate, the following items are required. Use of chloroquine phosphate 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 chloroquine phosphate. 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 chloroquine phosphate, and
    c. Informed that chloroquine phosphate is an unapproved 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 chloroquine phosphate.

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 chloroquine phosphate treatment within 7 calendar days from the onset of the event. The reports should include unique

identifiers and the words "**Chloroquine phosphate 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" a statement "**Chloroquine phosphate 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.

5. The prescribing health care provider and/or the provider's designee are/is responsible for submitting patient outcomes reports:
   - Complete and submit the report online: **Mandatory Patient Outcome Reporting Survey - EUA for Chloroquine Phosphate and Hydroxychloroquine Sulfate** https://euachloroquine-hydroxychloroquine-outcome.ppdi.com/.

APPROVED AVAILABLE ALTERNATIVES

There are no approved available alternative products. There is an EUA for treatment of the same population with hydroxychloroquine sulfate. 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 chloroquine phosphate 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 product chloroquine phosphate supplied from the Strategic National Stockpile for 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 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 chloroquine phosphate 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 chloroquine phosphate 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: **Chloroquine phosphate treatment under Emergency Use Authorization (EUA).**

This EUA for chloroquine phosphate 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.

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 weigh 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** and **CLINICAL OUTCOMES** 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.

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[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.
[2]

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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[2] 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.

5. The prescribing health care provider and/or the provider's designee are/is responsible for submitting patient outcomes:
   - Complete and submit the report online: **Mandatory Patient Outcome Reporting Survey - EUA for Chloroquine Phosphate and Hydroxychloroquine Sulfate** https://euachloroquine-hydroxychloroquine-outcome.ppdi.com/.

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.

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/s/

KAREN D WINESTOCK
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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Testing and Research
Division of Pharmaceutical Analysis

OTR-Technical Report

Date:	2020-03-27
From:	Douglas Kirkpatrick, (Chemist), CDER/OPQ/OTR/DPA, Jeffrey Woodruff, (Chemist), CDER/OPQ/OTR/DPA, Diem (Cindy) Ngo, (Chemist), CDER/OPQ/OTR/DPA, Li Tian, (Chemist), CDER/OPQ/OTR/DCDA
Through:	Connie Ruzicka, (Lab Chief, Branch I), CDER/OPQ/OTR/DPA
To:	Dr. Michael Kopcha, (Director), OPQ
Subject:	USP Compendial Analysis of Chloroquine Phosphate Tablets

Connie M. Ruzicka -S

Digitally signed by Connie M Ruzicka -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13003980978, cn=Connie M Ruzicka -S
Date: 2020.03.27 15:06:35 -05'00'

EXECUTIVE SUMMARY

Report Number: FY20-087-DPA-T

Personnel: Douglas Kirkpatrick, Jeffrey Woodruff and Diem Ngo, (OQP/OTR/DPA)
Li Tian, (OPQ/OTR/DPA)

Background: Preliminary clinical studies suggest that chloroquine phosphate may be used to help treat COVID-19. Should these studies be confirmed, the demand for chloroquine phosphate will increase rapidly. The FDA seeks to assess the quality of imported chloroquine phosphate tablets in the event that extra supply is needed.

Outcome/Impact: Results from this analysis will determine whether imported chloroquine phosphate tablets meet USP compendial standards. This outcome will impact the decision on whether or not these tablets are safe for US consumers.

Conclusion**:**

- All specifications for identification, assay, organic impurities, dissolution, and residual solvents were met for chloroquine phosphate tablets.
- ***Results indicate tablets meet USP compendial standards***.

Objective: To analyze chloroquine phosphate tablets for assay, identification, organic impurities, dissolution, and residual solvents using USP compendial methods.

Background: The current COVID-19 pandemic threatens the lives of millions and has led to devastating economic and societal impacts. Several preliminary studies indicate that the anti-malaria drug chloroquine phosphate may be used to help treat the virus. As a result, Bayer has provided the FDA with chloroquine phosphate tablets, an unapproved drug product in the US. These will be tested for quality in the case that further clinical studies confirm its efficacy treating COVID-19. This study seeks to perform analytical testing for the assay, organic impurities, dissolution and residual solvents of chloroquine phosphate tablets donated by Bayer.

Materials and Methods

1. Sample
   - Chloroquine phosphate tablets (250 mg), Bayer, Batch#GEQ0002AK, FACTS Sample#1142404

2. Methods
   - Identification, assay and dissolution testing were performed using the procedures defined in the USP monograph for chloroquine phosphate tablets.[1] There is no USP compendial method for impurities in chloroquine phosphate tablets. As a result, the USP impurity method for chloroquine phosphate substances was adapted. Samples were also analyzed for the presence of residual solvents following USP Chapter <467>.[3]

Results and Discussion

1. Identification

- From the UV-VIS: all samples were positively identified by comparison of the UV spectrum of the sample solutions at 343 nm and 329 nm to the UV spectrum of the USP chloroquine phosphate reference standard. **(PASS)**.
- From HPLC: the main peak from the sample solution has a similar retention time to the chloroquine phosphate peak in the standard solution **(PASS)**.

2. Assay

- The average potency of the chloroquine phosphate tablets was 98.0% and was within USP specification of 93.0-107.0%. **(PASS)**

3. Organic Impurities

- Since the impurity method was adopted from the drug substance monograph, it was important to first determine if excipients in the drug product overlapped with impurity peaks. Figure 1 shows a chromatogram for a standard solution containing all analytes at 2 µg/mL. Figure 2 shows an example chromatogram for the sample solution. The latter figure shows several unidentified peaks as well as two of the related impurities.

Importantly, there are no large excipient peaks that elute at the same time as impurities. This demonstrated specificity for use with tablets.

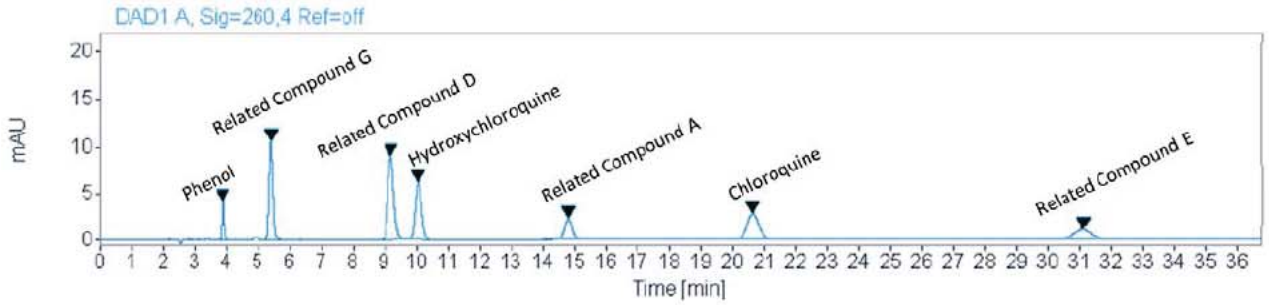

Figure 1: Chromatogram for the analysis of impurity standard solution

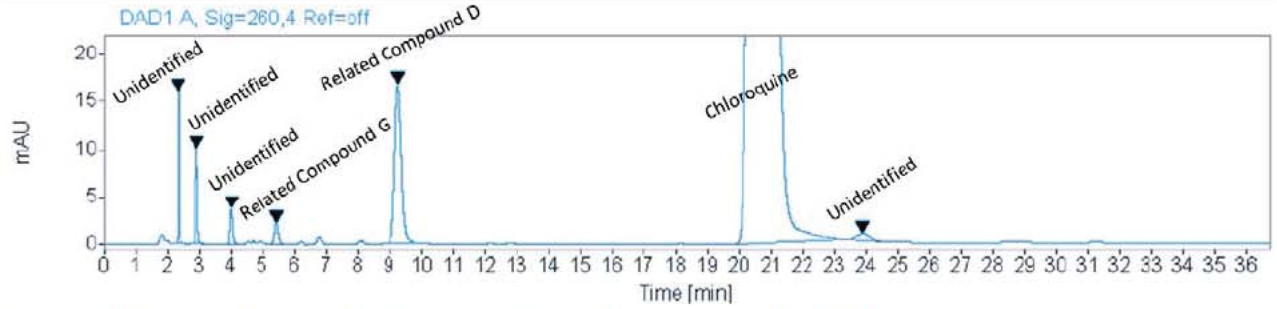

Figure 2: Chromatogram for the impurity analysis of sample solution

Results for the analysis of sample solutions are reported in Table 1. Here it shows that all specified impurities were below their respective specification limits. Additionally, all unidentified impurities were below the 0.1% threshold. Lastly, the total amount of impurities was below the 2.0% specification limit.

Table 1: Impurity content of chloroquine phosphate tablets

Compound	Avg (%)	Spec (%)	Result
Phenol	0.00	0.1	PASS
RC G	0.03	0.1	PASS
RC D	0.20	0.50	PASS
Hydroxychloroquine	0.00	0.1	PASS
RC A	0.00	0.1	PASS
RC E	0.00	0.1	PASS
Unspecified	0.05	0.10	PASS
Unspecified	0.06	0.10	PASS
Unspecified	0.03	0.10	PASS
Unspecified	0.03	0.10	PASS
Total Impurities:	0.39	2.0	PASS

It should be noted that the four compounds reported as unspecified impurities could be excipients. However, their measured amounts were so small that categorizing them as impurities did not impact the results of the analysis. The drug product **PASSED** impurity specifications.

4. **Dissolution**
   - Chloroquine phosphate tablets **PASSED** stage 1 dissolution testing and results are reported in Table 2. As an immediate release formulation, the tolerance is NLT 75% (Q) of the labeled amount dissolved at 45 minutes. The specification of passing stage 1 requires each unit to dissolve not less than Q+5% (80%) of the drug at 45 minutes.

Table 2: Dissolution results of chloroquine phosphate tablets

% Dissolved	Low (%)	High (%)	Mean (%)	SD (%)	%RSD	Specifications	Pass/Fail
101.0, 99.1, 98.2, 99.7, 97.9, 96.9	96.9	101.0	98.8	1.5	1.5	NLT 80%	Pass

5. **Residual Solvents**
   - Chloroquine phosphate tablets are water soluble, thus only Class 1, 2A and 2B residual solvents are of interest for this particular drug product. Class 1, 2A and 2B solvents and their USP concentration limits are listed in Table 3. Peaks for residual solvents (b) (4) were observed in the sample. (b) (4) is a Class 3 solvent and is regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known to be a human health hazard at levels normally accepted in pharmaceuticals. (b) (4) was present at concentrations below 5000 ppm, which is acceptable per USP specification. (b) (4) is a Class 2 solvent and was detected well below the USP exposure limit (b) (4) mg/day or (b) (4) ppm). Thus, the samples met the requirements of the USP residual solvents test.

Table 3: Control limits for residual solvents.

Class 1 Residual Solvents		
Solvent	**Concentration Limit (ppm)**	**Concern**
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard
Class 2 Residual Solvents		
Solvent	**PDE (mg/day)**	**Concentration Limit (ppm)**
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60

Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1	100
1,4-Dioxane	3.8	380
Hexane	2.9	290
Methanol	30	3000
Methylbutylketone	0.5	50
Methylene chloride	6	600
Nitromethane	0.5	50
Pyridine	2	200
Tetrahydrofuran	7.2	720
Tetralin	1	100
Toluene	8.9	890
Trichloroethylene	0.8	80
Xylene (m, p, o)	21.7	2170

References

1. USP42-NF37-941, Chloroquine Phosphate Tablets
2. USP40-NF35-3377, Chloroquine Phosphate
3. USP40-NF37 Chapter <467> Residual Solvents

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/s/

KAREN D WINESTOCK
03/29/2020 10:17:52 AM
Signatory for this review is Connie Ruzicka