Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection (PEPCOH)

NCT04372017

Protocol Document including SAP

Continuing Review Date 03.11.2021

Protocol Title

Post-Exposure Prophylaxis for COVID-19 with Hydroxychloroquine

Protocol Number: **PEPCOH**

Lead site Name: Sanford Health

Study Chair: Susan Hoover, MD

Version: 1.0 (2020.05.15)

NCT: 04372017

Responsibility Acknowledgement:

I have read this study protocol and agree to adhere to the requirements. I will provide copies of this study protocol and all pertinent information to the study personnel. I will discuss this material with them and ensure they are fully informed regarding the study interventions and the conduct of the study according to the Food and Drug Administration (FDA) Guidelines for Good Clinical Practices (GCP), the institutional policies and procedures, and pertinent individual country laws/regulations.

	Date
Site Principal Investigator	

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1.0 Protocol Summary

1.1 Synopsis

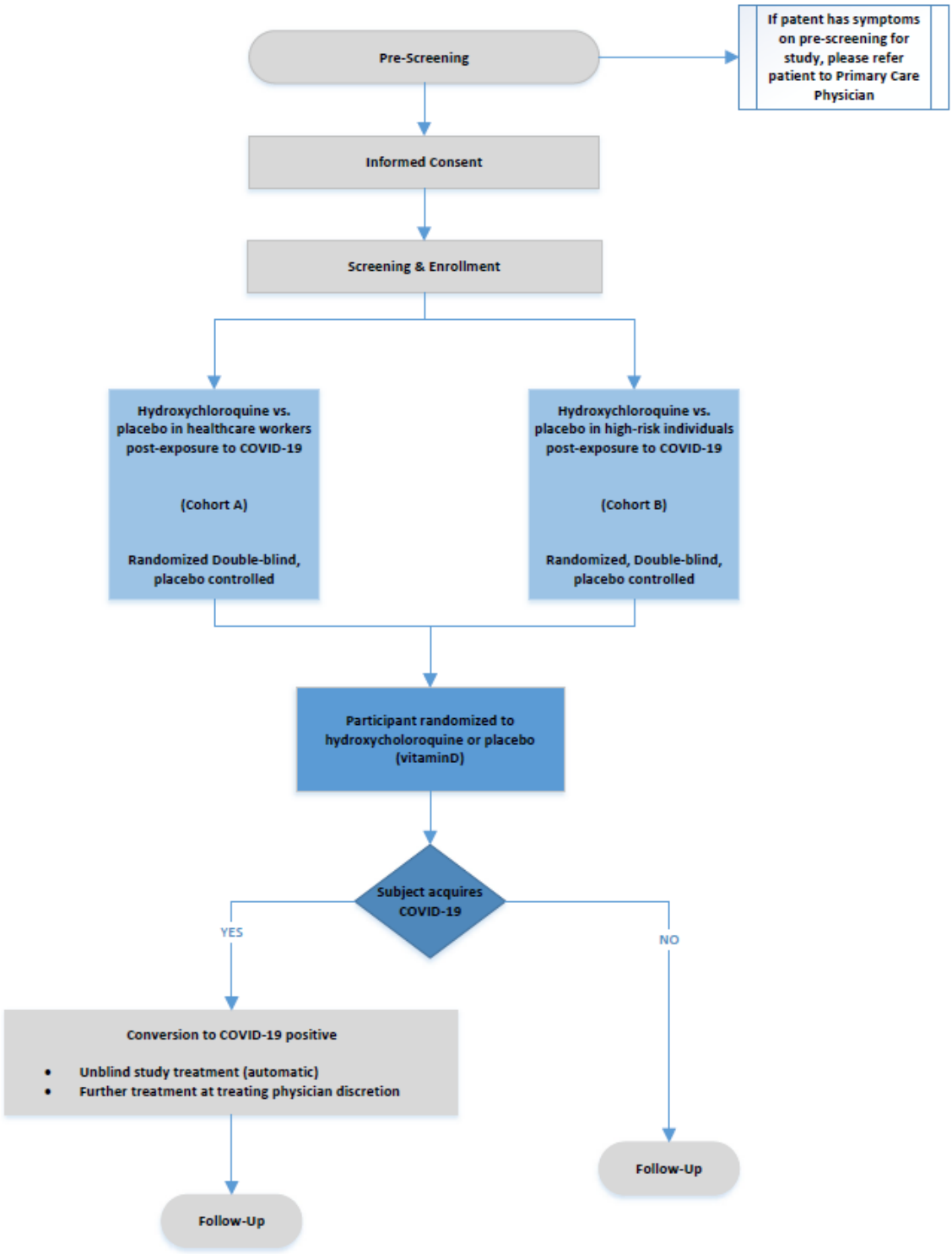
Title of Study	**Post-Exposure Prophylaxis for COVID-19 with Hydroxychloroquine (PEPCOH)**
Study Objectives	**Primary:** • Cohort A: Determine whether post-exposure prophylaxis with hydroxychloroquine can prevent COVID-19 in healthcare workers who have been exposed to a known case of COVID-19. • Cohort B: Determine whether post-exposure prophylaxis with hydroxychloroquine can prevent COVID-19 in high-risk individuals who have been exposed to a known case of COVID-19. **Primary Hypothesis:** • Cohort A: Primary Hypothesis: Hydroxychloroquine will reduce the number of healthcare workers that convert to infected status post-exposure compared with placebo. • Cohort B: Primary Hypothesis: Hydroxychloroquine will reduce the number of high-risk individuals that convert to infected status post-exposure compared with placebo.
Study Design	A multi-cohort, prospective, double-blind, randomized, placebo controlled study
Study Population	**Inclusion Criteria:** **Inclusion Criteria Cohort A:** • ≥ 18 years old • Employee of healthcare organization in South Dakota or Sanford Health employee in any location and with exposure to a person with COVID-19 within the last 5 days o Occupational exposure as determined by the participant's employee health department (i.e. not wearing the proper Personal Protective Equipment (PPE)) o Criteria according to Center for Disease Control (CDC) guidelines o Community exposure (within 6 feet for at least 15 minutes) • No current symptoms attributable to COVID-19, per HCW report (fever, cough, difficulty breathing, sore throat) • No prior COVID-19 positive diagnosis (eligible if previous testing is negative and meets all other inclusion and exclusion) • Ability to provide informed consent **Inclusion Criteria – Cohort B** • ≥ 18 years old • High-risk person who had close contact (i.e. within 6 feet for at least 15 minutes) with a COVID-19 positive person within the last 5 days and is a South Dakota resident or high-risk person with close household contact of a COVID-19 positive Sanford employee

	• High-risk person defined by:
	  • Age 18-44 with 2 or more comorbidities listed below
	  • Age 45-79 with any comorbid condition listed below
	  • Age 80 and above (regardless of comorbid conditions)
	  • Co-morbid list
	  o Congestive Heart Failure (CHF)
	  o Chronic lung disease[¥]
	  o Solid organ transplant or immunosuppression[*]
	  o Chronic Kidney Disease or End Stage Renal Disease
	  o Diabetes mellitus
	  o Cardiovascular disease/Hypertension
	  o Smoking/Vaping (currently using or history of using in the past 1 year)
	  o Obesity (calculated by height and weight per participant report)
	  o Hyperlipidemia
	[¥] *Includes any of the following: asthma, chronic obstructive pulmonary disease, emphysema*
	[*] *Defined as an outpatient prescription of greater than 10 mg/day of prednisone or equivalent, use of chemotherapy, or use of immunosuppressive agents for solid organ transplant or for an autoimmune disease.*
	• No current symptoms attributable to COVID-19
	• No prior COVID-19 positive diagnosis (eligible if previous testing is negative and meets all other inclusion and exclusion)
	• Ability to provide informed consent
	• Confirmed review of concomitant medications (with emphasis on cardiac medications)

	Exclusion Criteria: **Exclusion Criteria Cohort A & B:** • Known allergy to hydroxychloroquine or quinine • Known history of long QT syndrome • Known history of arrhythmia or dysrhythmia • Known current QTc >500 ms • Known G6PD deficiency • Known history of hypoglycemia • Pregnant or Nursing by patient history • Use of any of the following concomitant medications: See Appendix D for Exclusion medication list • Concurrent diagnosis of dermatitis, porphyria, or psoriasis • History of chronic liver disease, including cirrhosis and/or diagnosis of hepatitis (infectious, idiopathic, or immune) • History of chronic kidney disease • Pre-existing retinopathy • Already taking hydroxychloroquine • Any condition or medication in the opinion of the investigator that would prohibit the use of hydroxychloroquine • Enrollment in another clinical with investigational drug or device • Inability to swallow pills • Adults unable to provide informed consent

Sample Size	Cohort A n= 1356 Cohort B n= 383
Study Intervention	Hydroxychloroquine vs. Placebo (Vitamin D with calcium)
Study Evaluations	Assessments on this study will be completed as outlined in Section 8.3.
Study Period	Planned start date: April 2020 Planned accrual start date: April 2020 Planned accrual closure: April 2021 Planned study closure: April 2022

1.2 Schema



1.3 Schedule of Activities (SoA) Cohort A & B

This study consists of screening, enrollment and randomization, treatment, and follow-up. Follow-up will include evaluation of the treatment and subsequent infection, re-infection, adverse events, and long-term sequelae of treatment and/or infection. The detailed schedule of study procedures and assessments with the time intervals is shown in Table 1.

Table 1

	Screening & Enrollment		Treatment / Placebo Phase					Follow-up[b]		
Procedure	**Screening[a]**	**Enrollment / Randomization**	**Day 1**	**Day 2**	**Day 3[f]**	**Day 4**	**Day 5**	**Day 14 (± 1 day)**	**Day 35[e] (+3 days)**	**12 Months (±30 days)**
Informed Consent / HIPAA	X									
Inclusion/Exclusion	X									
Demographics	X									
Randomization		X								
Hydroxychloroquine / Placebo (Vitamin D with calcium)			X	X	X	X	X			
Patient Reported symptoms[c]					X		X	X	X	
Adverse Event Assessment					X		X	X	X	X
Outcomes[d]								X	X	X

a. Screening must be completed within 48 hours prior to study enrollment

b. Follow-up visits will consist of a phone call to the patient. Hydroxychloroquine and placebo patients will be followed.

c. Includes: patient reported temperature, cough, difficulty breathing, sore throat, chills, muscle pain, headache, new loss of taste or smell, and diarrhea.

d. Did the patient acquire COVID-19?

e. Day 35 should be at least 30 days (+3 days) post last dose of drug.

f. Day 3 and 5 AE assessment via phone call. (window ±1day)

2.0 Introduction

2.1 Study Rationale

Currently, prevention of person-to-person transmission of SARS-CoV-2, the virus which causes COVID-19, is achieved by reducing close contact through physical distancing measures and through the use of personal protective equipment (PPE) in the healthcare setting. The effect of post-exposure medication treatment on acquisition of infection or progression to symptomatic disease is unknown.

2.2 Background

Coronavirus Infectious Disease-2019 (COVID-19) is an infection caused by a novel virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which emerged in the winter of 2019 initially in China, then spread to involve the entire world in a pandemic. Infected individuals may be asymptomatic, while others demonstrate a range of symptoms from upper respiratory symptoms to pneumonia, respiratory failure, acute respiratory distress syndrome, or death. Hydroxychloroquine inhibits SARS-CoV-2 replication in vitro and may have antiviral effects in people with COVID-19 disease (Yao *et al*. 2020). It is postulated that early preemptive therapy may prevent disease or reduce severity, but its effectiveness in the post-exposure setting is unknown.

3.0 Objectives and Endpoints

3.1 Primary Objectives

- Cohort A: Determine whether post-exposure prophylaxis with hydroxychloroquine can prevent COVID-19 in healthcare workers with direct patient contact who have been exposed to a known case of COVID-19.
- Cohort B: Determine whether post-exposure prophylaxis with hydroxychloroquine can prevent COVID-19 in high-risk individuals who have been exposed to a known case of COVID-19.

3.2 Primary Hypothesis:

- Cohort A: Primary Hypothesis: Hydroxychloroquine will reduce the number of healthcare workers that convert to infected status post-exposure compared with placebo.
- Cohort B: Primary Hypothesis: Hydroxychloroquine will reduce the number of high-risk individuals that convert to infected status post-exposure compared with placebo.

4.0 Study Design

4.1 Overall study design

This is a prospective, double-blind, randomized, placebo-controlled study in two distinct cohorts to evaluate the efficacy and safety of hydroxychloroquine in the prevention of COVID-19 infection. Additional sub-studies will be added and removed throughout this larger "tent" protocol to answer other objectives. These studies will be listed in the appendices of this protocol.

Other non-Sanford institutions will be allowed to participate in this study after all legal and regulatory documents are final.

Sanford Health will function as the lead site for trial oversight.

4.2 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including last follow up visit at 12 months.

5.0 Study Population

5.1 Inclusion Criteria

See Synopsis (section 1.1)

5.2 Exclusion

See Synopsis (section 1.1)

5.2 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information should include demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Screen failures will not count towards total enrollment.

6.0 Study Intervention

6.1 Study Intervention(s) Administered:

Hydroxychloroquine/placebo (vitamin D with calcium) will be administered as part of this study. Randomization will occur at a 1:1 ratio in each cohort. Participation in additional non-interventional clinical research studies is allowed. If the participant becomes infected with COVID-19, the participant will stop the intervention and be treated per the discretion of their primary care provider.

Subjects enrolled will be assigned to the appropriate cohort and randomized to receive hydroxychloroquine 200mg tablets, Day 1 – 2 tablets by mouth twice per day, Day 2-5 1 tablet by mouth twice per day (total of 12 tablets) or placebo. Placebo will be vitamin D with calcium tablets 10mcg tablet - Day 1 – 2 tablets by mouth twice per day, Day 2-5 1 tablet by mouth twice per day (total of 12 tablets). Subjects will be monitored for any toxicities during and after treatment.

Table 2. Intervention dosing

Drug	Dose	Dose Frequency	Route
Hydroxychloroquine 200 mg tablets	2 tablets	Twice daily on day 1	PO
	1 tablet	Twice daily on days 2-5	PO
Placebo (vitamin D with calcium, 10mcg/25mg tablets)	2 tablets	Twice daily on day 1	PO
	1 tablet	Twice daily on days 2-5	PO

6.2 Hydroxychloroquine Sulfate (See Appendix C for more information)

6.2.1. Other Names
IUPAC: 2-[4-[(7-chloroquinolin-4-yl)amino]pentyl-ethylamino]ethanol
MeSH: Plaquenil; Hydroxychlorochin; Hydroxychloroquine; Hydroxychloroquine Sulfate: Hydroxychloroquine Sulfate (1:1) Salt; Oxychlorochin; Oxychloroquin; 4-aminoquinoline

6.2.2. Classification
Immunosuppressive, anti-inflammatory, anti-autophagy, and anti-malarial

6.2.3. Dose Specifics
One tablet of 200 mg of hydroxychloroquine sulfate is equivalent to 155 mg base. See section 6.1 for dosing.

6.2.5. Preparation
No special preparation.

6.2.6. Administration
Take hydroxychloroquine sulfate by mouth, preferably with a meal or a glass of milk.

6.2.7. Contraindications
Use of hydroxychloroquine sulfate is contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds. Use with

caution in patients with alcoholism, hepatic/renal dysfunction, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, gastrointestinal, neurological, or blood disorders. A dose reduction may be required.

6.2.8. Availability

Commercially available as a tablet for oral administration. For the purposes of this study the tablet drug will be provided by Sanford Research and supplied in 200mg tablets with matching placebo.

6.2.9. Side Effects

1. Ocular:
   It is recommended that hydroxychloroquine be discontinued if ocular toxicity is suspected and the patient should be closely observed given that retinal changes (and visual disturbances) may progress even after cessation of therapy.

   Retinal toxicity from hydroxychloroquine is serious but very rare. The incidence rises sharply to about 1% at 5 years of use, so the American Academy of Ophthalmology recommends screening starting after 5 years. Toxicity is more common with doses exceeding 400 mg/day or a total dose of more than 1000 g. This study dose is 800 mg for 1 day then 400 mg for 4 more days (Marmor *et al.* 2011).

2. Cardiac: Post marketing cases of life-threatening and fatal cardiomyopathy have been reported with use of hydroxychloroquine sulfate. Patients may present with atrioventricular block, pulmonary hypertension, and sick sinus syndrome or with cardiac complications. Electrocardiogram (ECG) findings may include atrioventricular, right or left bundle branch block. Signs or symptoms of cardiac compromise have appeared during acute and chronic treatment. Clinical monitoring for signs and symptoms of cardiomyopathy is advised. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrio-ventricular heart block) or biventricular hypertrophy are diagnosed. If cardiotoxicity is suspected, prompt discontinuation of hydroxychloroquine sulfate may prevent life-threatening complications.

   Hydroxychloroquine sulfate prolongs the QT interval. Ventricular arrhythmias and torsades de pointes have been reported in patients taking hydroxychloroquine. Therefore, hydroxychloroquine sulfate should not be administered with other drugs that have the potential to prolong the QT interval.

Hydroxychloroquine has been used for decades for malaria and autoimmune disease without pre-treatment EKGs or routine cardiac monitoring. A 2018 review of short-term antimalarial treatment including chloroquine, which is known to carry greater risk of toxicity, found no serious cardiac adverse events among participants (n=1076), receiving acute therapy for malaria. With chronic use of hydroxychloroquine (years), QT prolongation and cardiomyopathy have occurred. This study uses a 5-day course and subjects with heart disease will be excluded (Haeusler et al. 2018).

3. 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. The preparation should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the possible hazard.

4. 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, have been reported. Muscle and nerve biopsies have been associated with curvilinear bodies and muscle fiber atrophy with vacuolar changes. Assess muscle strength and deep tendon reflexes periodically in patients on long-term therapy with hydroxychloroquine sulfate.

5. Neuropsychiatric Events, Including Suicidality: Suicidal behavior has been rarely reported in patients treated with hydroxychloroquine sulfate.

6. Hypoglycemia: Hydroxychloroquine sulfate has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with or without antidiabetic medications. Patients treated with hydroxychloroquine sulfate should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with hydroxychloroquine sulfate should have their blood glucose checked and treatment reviewed as necessary.

7. Dermatologic Effects: Dermatologic reactions to hydroxychloroquine sulfate may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

6.3 Vitamin D with calcium (Cholecalciferol)

6.3.1 Other Names IUPAC Name: (1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol

MeSH: (3 beta,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol; Calciol; Cholecalciferol; Vitamin D3

6.3.2 Classification Lipophilic secosteroid

6.3.3 Mode of Action

Vitamin D with calcium is dietary supplement used to promote calcium absorption in intestines, bone resorption, increase phosphate levels to maintain skeletal calcium balance. *In vivo* synthesis of the major biologically active metabolites of vitamin D with calcium occurs in two steps. First, in the liver microsomal enzymes convert vitamin D to calcifediol (25-hydroxycholecalciferol). Second, calcifediol is released into systemic circulation where it binds vitamin D-binding protein, an α-globulin carrier protein that transports it to the proximal tubules of the kidneys where Parathyroid hormone regulates its further hydroxylation to calcitriol (1,25-dihydroxycholecalciferol). Calcitriol is again released into systemic circulation, binds to vitamin D-binding protein and is distributed to throughout the body including to target organs like intestine, kidney, and bone. Vitamin D is indicated in treatment of hypoparathyroidism, refractory rickets, and familial hypophosphatemia.

Vitamin D3 and vitamin D2 are bioequivalent.

6.3.4 Storage and Stability

Vitamin D3 with calcium tablets are stored at room temperature 15°-30°C (59°-86°F), protect from light and moisture. They should be dispense in a tight, light-resistant container.

6.3.5 Dose Specifics

Placebo will be vitamin D with calcium tablets 10mcg/25mg tablet. See section 6.1 for dosing.

6.3.6 Preparation

No special preparation.

6.3.7 Administration

Take Vitamin D3 with calcium by mouth with meal or a glass of milk.

Take hydroxychloroquine sulfate by mouth, preferably with a meal or a glass of milk.

6.3.8 Contraindications:

Use of Vitamin D3 with calcium is contraindicated in patients with renal impairment, heart disease, kidney stones, arteriosclerosis, and individuals with hypercalcemia, hypervitaminosis D; gastrointestinal, liver, or biliary disease associated with malabsorption of vitamin D analogues and drugs that could have allergenic cross reactivity/hypersensitivity with Vitamin D3.

6.3.9 Availability

Commercially available as a tablet for oral administration. For the purposes of this study the tablet drug will be provided by Sanford Research and supplied in 10mcg/25mg tablets as placebo.

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6.3.10 Side Effects

1. Renal: Impairment of renal function with polyuria, nocturia, polydipsia, hypercalcemia, reversible azotemia, hypertension, nephrocalcinosis, generalized vascular calcification, or irreversible renal insufficiency which may result in death
2. Central Nervous System (CNS): Mental retardation, disorientation, confusion
3. Soft Tissues: widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs
4. Skeletal: Bone demineralization (osteoporosis) in adults. Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism), vague aches, stiffness, and weakness
5. Gastrointestinal: Nausea, anorexia, and constipation
6. Metabolic: Mild acidosis, anemia, and weight loss
7. Teratogenic effects: supravalvular aortic stenosis, elfin facies, and mental retardation recorded in pregnant women with hypervitaminosis D

6.4 Participant Implications

1. If a participant vomits after taking their dose study drug it will be considered a missed dose and not retaken. The participant will resume with the next scheduled dose.
2. If the participant forgets to take a dose, that dose will not be made up and participant will resume with the next scheduled dose.
3. If the participant is unable to start the hydroxycholoroquine / vitamin D with calcium in the morning on Day 1 due to delivery timing, the participant is allowed to initiate Day 1 with an evening dose.
4. Participants should have at least 8 hours between doses.

5. Participants will be instructed to inform the study coordinator of any medication changes while on the active phase of the study

6.5 Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed.

6.6 Measures to Minimize Bias: Randomization and Blinding

On enrollment day, the participant will be assigned a unique number (randomization number). The randomization number encodes the participant's assignment to hydroxychloroquine or placebo (vitamin D with calcium), according to the randomization schedule generated prior to the study by the Sanford Command Core. Each participant will be dispensed randomized study intervention, labeled with his/her unique randomization number, throughout the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.7 Study Intervention Compliance

A pill diary will be given to each enrolled participant to document pill compliance.

6.8 Concomitant Therapy

- See inclusion and exclusion criteria for medications that are not allowed.
- No washout period is needed for hydroxychloroquine.
- Vaccines are allowed while on the study.

6.9 Intervention after the End of the Study

Participants who acquire COVID-19 while on study intervention as determined by a positive test indicating COVID-19 will be instructed to discontinue the study intervention by the study team. Participants will be unblinded and subsequent treatment will be at the discretion of their primary care physician or provider who ordered the COVID-19 testing.

7.0 Participant Discontinuation/Withdrawal

Participants may withdraw consent at any time for any reason or be withdrawn from the trial at the discretion of the investigator should any untoward effect occur. In addition, a participant may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

7.1 Discontinuation of Study Intervention:

A participant must be discontinued from the trial for any of the following reasons:

- The participant withdraws consent.
- Intercurrent illness that prevents further administration of treatment
- The participant has a confirmed positive pregnancy test
- The participant is lost to follow-up

At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

For those participants who discontinue study intervention early, each participant will be followed for 30 days for acute adverse event monitoring.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, any data collected be for that time may be retained.

7.3 Lost To Follow Up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.

Lost to follow-up is defined by:

- The inability to reach the participant after a minimum of two documented phone calls and
- Lack of response by participant to one certified mail letter.

All attempts should be documented in the participant medical record. Should the participant continue to be unreachable, he/she will be considered lost to follow up. Outcome information that is available via electronic medical records will be documented if available.

If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death.

8.0 Study Procedures and Safety Assessments

8.1 Administrative Procedures

8.1.1 Screening Procedures

All participants must agree to participate in the study prior to any study specific screening procedures being performed. Every participant shall be provided an Institutional Review Board (IRB)-approved informed consent to review and keep for his/her records.

Once consent has been documented, the site will assign the participant a screening number. A Screening Log of consented patients will be maintained at each site.

Screening evaluations will be used to determine the eligibility of the participant for study inclusion. All screening activities must be completed within 48 hours prior to study enrollment and include the following:

- Inclusion/Exclusion Criteria
- Demographics and Medical History

All screening evaluations must be completed and reviewed by the site investigator or healthcare licensed designee to confirm that potential participants meet all eligibility criteria. The study team will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1.2 Informed Consent

A study team member must obtain documented consent from each potential participant prior to participating in a clinical trial. This study will utilize an electronic consent process based in REDCap, a CFR part 11 compliant research database. An electronic version of the informed consent form will be approved by the IRB prior to use. When a participant is contacted for enrollment into the study, an email containing a unique link will be generated by REDCap and sent to the patient while on the phone with a study team member. A password will be provided to the participant verbally over the phone that is required to access the informed consent. This provides confirmation of the identity of the participant. Once the informed consent form has successfully accessed, the study team member will allow a period of time of 1-4 hours for the participant to read the informed consent and formulate questions. The study team member will place another call with the participant and proceed to have an informed consent discussion, answering any questions the participant might have. If the participant is willing to participate in the study, he or she will proceed to provide an electronic signature using a mouse or their finger and save the document. This locks the document from any further changes. An email containing a copy of the signed informed consent form will be generated via REDCap and emailed to the participant. A PDF of the signed informed consent document will be saved in the participant's medical record as well as printed out for the study file.

A copy of the consent form will be automatically generated via REDCap and emailed to the participant before participation in the trial. The research team member who obtained consent will record the consenting process per their institutional guidelines.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB's approval in advance of use. The participant will be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The informed consent will adhere to IRB requirements, applicable laws and regulations.

8.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the site Principal Investigator (PI) or licensed designee to ensure that the participant qualifies for the study.

8.1.4 Assignment of Screening Number

Consented participants will be assigned a screening number.

8.1.5 Enrollment

Once all screening procedures have been completed the site PI or licensed designee (RN, CNP, pharmacist, or physician) on the study team will review acknowledge the inclusion/exclusion source document. If the potential participant is determined to be eligible, the study site will enroll the participant in appropriate cohort in the electronic data capture (EDC) and then randomized by the Sanford Command Core to the intervention assignment. Sites will be notified by email in real time the randomization confirmation. The site study team will maintain an enrollment log and the lead site will maintain a study-wide enrollment log. If the potential participant is not eligible and becomes a screen fail, the reason will be noted on the inclusion/exclusion in the EDC and filed in the study records.

8.1.6 Assignment of Study Participant Number

Participants will be assigned a participant study number at enrollment at the same time as randomization by the EDC. This number will be unique to this participant.

8.2 Clinical Procedures/Assessments

See Schedule of events for activities that need to be done at each visit.

8.2.1 Participant Reported Outcomes

Participant self-reported COVID-19 symptoms (temperature, cough, difficulty breathing, and sore throat) will be collected by the study team at time points outlined in the SoA. Participants will also be asked if they have or are

currently experiencing any other symptoms since starting the study intervention. These will be included in the adverse event monitoring.

8.2.2 Adverse Event (AE) Monitoring

The investigator or licensed designee (RN, CNP, pharmacist, or physician) on the study team will assess each participant to evaluate for potential new or worsening AEs as specified in the SoA and more frequently if clinically indicated. If participant reported symptoms are an AE, the event will be tracked as an AE.

Participants will be followed and accessed for acute AEs until day 35 (30 days after the last dose of study medication). AEs will be documented accordingly. Adverse events will also be assessed at the 12 month follow up visit.

8.3 Adverse events and Serious Adverse Events (SAE):

An AE is defined as any untoward or unfavorable medical occurrence in human participants, including any abnormal sign, symptom, or disease, temporally associated with the participant's participation in the research, whether considered related to the participant's participation in the research or not. AEs encompass both physical, psychological harms, and biochemical abnormalities. AEs may be reported by the participant, observed by the Investigator, or documented in medical records.

The site investigator and any licensed designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study treatment. The site investigator or licensed designee will evaluate all adverse events according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Toxicities will be characterized in terms regarding grade (seriousness), causality/attribution (see section 8.3.2), and action taken with regard to trial intervention.

Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

If the adverse event meets any of the criteria below, it is regarded as a SAE:

- the event led to the death of the participant
- the event led to serious deterioration in the health of the participant, that either resulted in:
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or a body function
    - in-patient or prolonged hospitalization

- an important medical event- defined as an event requiring medical or surgical intervention to prevent one of the outcomes listed above in this definition.

8.3.1 AE and SAE Collection and Reporting

All acute SAEs/AEs will be collected from the time the informed consent form (ICF) is signed until day 35. Follow-up of AEs will end either when the symptom or illness resolves completely, up to 30 days past the end of study participation (if ongoing at the time of study exit) or until the investigator determines that the event has stabilized and will not completely resolve. Participants will be assessed at the 12 month visit for any potential adverse events that could be attributable to hydroxychloroquine.

AEs to be reported include:

- All SAEs regardless of attribution
- All Cardiac AEs for Grade 2 and above that are attributed to intervention (possible, probable, and definite)
- All AEs grade 3 and above regardless of attribution

Enrollment will be held and the SRC committee will meet if the following occur:

- Any SAEs with an attribution of possible, probable, and definite
- Any Cardiac AEs for Grade 2 and above that are attributed to intervention (possible, probable, and definite)
- Any AEs grade 3 and above attributed to intervention (possible, probable, and definite)

The SRC will review safety data and determine if the study can continue.

8.3.2 AE/SAE Assessments

All AE and SAE reporting will be conducted in compliance Sanford Health Policy HRP 024 New Information.

AE assessments will be focused on body systems with potential known toxicities and well as other toxicities verbalized by the participant.

All AE and SAEs will be assigned causality by the Investigator in their relationship to the study medication based on the following categories:

- Definitely: clear evidence exists that the event was caused by the intervention
- Probably: reasonable probability exists that the event was caused by the intervention
- Possibly: reasonable possibility exists that the event may have been caused by the intervention
- Unlikely: evidence exists that the event was caused by other factors; although the relationship of the event to the intervention cannot be completely ruled out, is remote

- Unrelated: the cause of the event is known and the event is in no way related to any aspect of the intervention

SAEs must be reported to the lead site and study chair at SH_HCQ_Team@sanfordhealth.org as soon as possible, but no later than 24 hours from the day the study team became aware of the event. Follow-up reports may be required or requested by the lead site or regulatory agency and should be completed promptly.

IRB notification of SAEs is required per Sanford IRB reporting guidelines. Investigators and study personnel are responsible for knowing IRB reporting requirements. Reporting of SAEs, whether related or unrelated to the study participation, should follow the most stringent rules for reporting.

The date of onset of the event, the date the site staff became aware of the event and determined it met the criteria of an SAE, and the date the event resolved or no longer fit the criteria of SAE will be documented in the source document and in the EDC system.

8.3.3 Safety Review Committee (SRC)

An independent SRC will be established with experienced members, none of whom are participating as study investigators, to monitor and evaluate the safety of subjects, to maintain oversight of study data and to monitor progress of the study. The committee will initially meet monthly and more frequently if concerns of safety are noted. The findings of the SRC will be submitted to the IRB within 10 days after the meeting. All SAEs will be reported to the SRC as soon as possible after learning of the event.

The Study Chair will review cumulative AEs and SAEs weekly and will share concerns with the SRC. The SRC will make recommendations to the Study Chair regarding steps to ensure subject safety and the continued ethical integrity of the trial. The SRC will review interim study results and consider the overall risk and benefit to trial participants. The SRC will recommend to the Study Chair whether the trial should continue in accordance with the protocol.

9.0 Statistical Considerations

9.1 Statistical Hypothesis

There will be a 50% decrease (relative risk reduction) in the conversion to infected status within the treatment arm compared to the control arm.

9.2 Sample Size Determination

Cohort A:

It is expected that 10% of exposed healthcare workers will convert to infected status without intervention. The treatment arm will be assumed to have a conversion of 5% (50% relative reduction, 5% absolute risk reduction). Due to the uncertainty of this

trial, a conservative 10% drop out rate is included in the calculation. Under these assumptions (Treatment: 5% infected, Control: 10% infected, α: 0.0492, Power: 90%), the total sample size is 1356 patients (610 patients are needed in each arm + 10% dropout = 1356 total patients).

Cohort B:

It is expected that 30% of exposed high risk patients will convert to infected status without intervention. The treatment arm will be assumed to have a conversion of 15% (50% relative reduction, 15% absolute risk reduction). Due to the uncertainty of this trial, a conservative 10% drop out rate is included in the calculation. Under these assumptions (Treatment: 15% infected, Control: 30% infected, α: 0.0492, Power: 90%), the total sample size is 383 patients (172 patients are needed in each arm + 10% dropout = 383 total patients).

9.3 Statistical Analyses

All baseline and demographic variables such as race, gender, age, height, and weight will be summarized. Continuous variables will be summarized using mean, standard deviation, median, IQR, minimum and maximum. Categorical variables will be presented using frequencies and percentages.

Difference in infected status proportions between the treatment and control groups will be evaluated using Fisher's exact test. The number of adverse events, rate of occurrence, and severity by treatment group will be reported and statistically compared using non-parametric methods.

Details of the analysis methods will be provided in the Statistical Analysis Plan (SAP), which will be finalized as early as possible after enrollment commences in order to minimize bias in the analysis strategy.

9.4 Interim Analysis

An interim analysis will be conducted to determine if the study should be stopped due to safety concerns or efficacy. Using O'Brien-Fleming approach, the interim analysis will use a significance level of $\alpha = 0.0054$ and the final analysis will use a significance level of 0.0492. The interim safety analysis will be performed when 50% of subjects, within their respective cohort, complete their 35 day follow-up. Overall safety will be analyzed first, and if safety outcomes are statistically higher in the treatment group ($\alpha = 0.0054$), enrollment will be stopped, participants will be unblinded and each cohort will be analyzed independently. If safety has not been compromised the study maybe resumed after review and recommendation by the SRC. Efficacy will be analyzed for early declaration of success. If power of 90% has been detected and a statistically significant change has been identified ($\alpha = 0.0054$), that specific cohort will stop enrollment and the final analysis will be done with completed data from participants enrolled at that time, otherwise the study will continue enrolling patients and final analysis will be completed.

10.0 Regulatory, Ethical, and Study Oversight

10.1 Statement of Compliance

This study will be conducted in accordance with this protocol, FDA and applicable local regulatory requirements.

Before enrollment of participants into this study, the IRB will review and approve the protocol, informed consent documents, any promotional material/advertisements, and any other written information to be provided to the participants. The Package Insert for hydroxychloroquine describing the investigational product will be provided to the IRB for review, see Appendix C. Drug information for vitamin D with calcium is provided in Section 6.3. Also see Appendix D. The IRB's composition or a statement that the IRB's composition meets applicable regulatory criteria will be documented.

If the protocol or any other information given to the participant is amended, the revised documents will be reviewed and approved by the IRB, where applicable. The protocol amendment will only be implemented upon the lead site's receipt of approval and, if required, upon the lead site's notification of applicable regulatory authority(ies) approval except for changes necessary to eliminate an immediate hazard to study participants.

10.2 Informed Consent

Written informed consent will embody the elements of informed consent as required by 21 CFR 50.27 and the IRB and will be in accordance with all applicable laws and regulations. Site investigators will enroll participants according to the study eligibility criteria and in compliance with 21 CFR 50, Protection of Human Participants. The investigator will exercise no selectivity so that no bias is introduced from this source.

The site investigator or qualified study team member must obtain documented consent from each potential participant prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (e.g., health or age of majority requirements), the investigator or study team member delegated this task must ensure the appropriate consent is in place.

A copy of the consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive Sanford IRB's approval in advance of use. The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be documented in the participant's study chart. Communication may take place in person, over the telephone or by mail.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

10.3 Study Participant Confidentiality

The investigator will comply with applicable participant privacy regulations/guidance as described as per the Health Insurance Portability and Accountability Act (HIPAA) and any additional local regulations.

The lead site is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, lead site (or representative), IRB, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

The participant must be informed that his/her personal study-related data will be used by the lead site in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Research Staff for quality data review at each site or other authorized personnel appointed by the lead site, by appropriate IRB members, and by inspectors from regulatory authorities.

10.4 Risks and Benefits

Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from a trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

10.5 Ethics

The study protocol, along with the required informed consent forms, will be approved by the Sanford IRB prior to the initiation of any research procedures (at the site). In addition to details described in the sections above (informed consent, confidentiality, and risks and benefits), the investigators should review and consider ethical ramifications in the design and development of this protocol, in accordance with 21 CFR 50. Protections of Human Participants. The investigators will make every effort to minimize and monitor risks and discomforts to participants throughout the course of the study.

10.6 Study Documentation and Case Report Forms (CRFs)

The data collection tool for this study will be defined CRF/eCRFs to be completed by study-site personnel. The investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include medical records/electronic medical records, records detailing the progress of the study for each participant, signed informed consent forms, drug disposition records, correspondence with the IRB and the study monitor/lead site, screening and consent information, CRFs/eCRFs, AE/SAE reports, laboratory reports, participant diaries/questionnaires, data clarifications requested by the lead site study team, and any other documentation

deemed relevant and pertinent to the study and the study participants. Participant data necessary for analysis and reporting will be entered into a validated database or data system in accordance with Title 21 of the Code of Federal Regulations (21 CFR) Part 11. The site investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs/eCRFs.

10.7 Document and Data Retention

Health information will be used to conduct this study to determine research results. Health information is used to report results of research to federal regulatory agencies, if applicable. Health information from study participants may be included in an audit to ensure that the study follows regulations, policies, and study plans.

All records will be maintained indefinitely. Sanford policy on record retention and destruction specific to research studies will be followed for Sanford sites. Non-Sanford sites will follow their policy for record retention and destruction Clinical data will be stored indefinitely. If a subject chooses to withdrawal consent to the study, he/she may request to withdraw. No further data will be collected on the subject, but any data collected prior to withdrawal will be and used for analysis.

The site will retain study documentation and data (electronic case report forms) in accordance with applicable regulatory requirements and each site document and data retention policy.

10.8 Direct Access to Source Data/Documents

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for quality data review by the study team at each site, audits by the lead site or lead site's representatives, review by the IRB, and inspections by applicable regulatory authorities. If contacted by an applicable regulatory authority, the investigator will notify the lead site of contact, cooperate with the authority, provide the lead site with copies of all documents received from the authority, and allow the lead site to comment on any responses.

10.9 Protocol Compliance

Deviations from the approved study protocol will be noted by study staff and will be reported to the IRB by the investigator/treating physician per Sanford IRB policy HRP 024 New Information for reporting protocol deviations/violations.

10.10 Publication Policy

Manuscript submission for publication of the results of this study, or any aspect of work directly related to the study, will be decided by the investigators. Any investigator can submit a publication concept proposal including proposed authorship order to the rest of the investigators for review, which will take place within 30 days after a proposal has been submitted.

Appendix A: Abbreviations

AE / SAE	Adverse Event / Serious Adverse Event
BCVA	Best Corrected Distance Visual Acuity
CTCAE	Common Terminology Criteria for Adverse Events
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CNS	Central Nervous System
COVID	Coronavirus Disease
CRF / eCRF	Case Report Form / Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Guidelines for Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
NCI	National Cancer Institute
PI	Principal Investigator
PO	By Mouth
PPE	Personal Protection Equipment
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD-OCT	Spectral Domain Ocular Coherence Tomography
SoA	Schedule of Activities
SOC	Standard of Care
SRC	Safety Review Committee
VF	Visual Field

Appendix B: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
[Amendment X]	*[Day-Mon-Year]*
[Amendment X]	*[Day-Mon-Year]*
[Amendment X]	*[Day-Mon-Year]*
Original Protocol	*[Day-Mon-Year]*

Amendment X

Overall Rationale for the Amendment: (Primary reason for this amendment at the top)

Section # and Name	Description of Change	Brief Rationale
[INSERT]	[INSERT]	[INSERT]
[INSERT]	[INSERT]	[INSERT]
[INSERT]	[INSERT]	[INSERT]

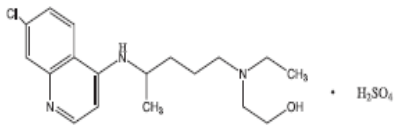
Appendix C: Hydroxychloroquine Drug Information

Hydroxychloroquine Sulfate Tablets, USP

200 mg

℞ only

DESCRIPTION: Hydroxychloroquine sulfate, USP is a white or practically white, crystalline powder, freely soluble in water; practically insoluble in alcohol, chloroform, and in ether. The chemical name for hydroxychloroquine sulfate is 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl] ethylamino] ethanol sulfate (1:1). Its structural formula is:



The molecular weight of hydroxychloroquine sulfate is 433.96, and molecular formula is $C_{18}H_{26}ClN_3O \cdot H_2SO_4$.

Hydroxychloroquine sulfate tablets, USP contain 200 mg hydroxychloroquine sulfate, USP equivalent to 155 mg base, and are for oral administration.

Inactive ingredients: anhydrous lactose, croscarmellose sodium, glyceryl triacetate, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY: Pharmacokinetics: Following a single 200 mg oral dose of hydroxychloroquine sulfate tablets to healthy males, the mean peak blood concentration of hydroxychloroquine was 129.6 ng/mL, reached in 3.26 hours with a half-life of 537 hours (22.4 days). In the same study, the plasma peak concentration was 50.3 ng/mL reached in 3.74 hours with a half-life of 2963 hours (123.5 days). Urine hydroxychloroquine levels were still detectable after 3 months with approximately 10% of the dose excreted as the parent drug. Results following a single dose of a 200 mg tablet versus I.V. infusion (155 mg), demonstrated a half-life of about 40 days and a large volume of distribution. Peak blood concentrations of metabolites were observed at the same time as peak levels of hydroxychloroquine. The mean fraction of the dose absorbed was 0.74. After administration of single 155 mg and 310 mg intravenous doses, peak blood concentrations ranged from 1161 ng/mL to 2436 ng/mL (mean 1918 ng/mL) following the 155 mg infusion and 6 months following the 310 mg infusion. Pharmacokinetic parameters were not significantly different over the therapeutic dose range of 155 mg and 310 mg indicating linear kinetics.

Following chronic oral administration of hydroxychloroquine, significant levels of three metabolites, desethylhydroxychloroquine (DHCQ), desethylchloroquine (DCQ), and bidesethylhydroxychloroquine (BDCQ) have been found in plasma and blood, with DHCQ being the major metabolite. The absorption half-life was approximately 3 to 4 hours and the terminal half-life ranged from 40 to 50 days. The long half-life can be attributed to extensive tissue uptake rather than through decreased excretion. Peak plasma levels of hydroxychloroquine were seen in about 3 to 4 hours. Renal clearance in rheumatoid arthritis (RA) patients taking hydroxychloroquine sulfate tablets for at least six months seemed to be similar to that of the single dose studies in volunteers, suggesting that no change occurs with chronic dosing. Range for renal clearance of unchanged drug was approximately 16% to 30% and did not correlate with creatinine clearance; therefore, a dosage adjustment is not required for patients with renal impairment. In RA patients, there was large variability as to the fraction of the dose absorbed (i.e., 30% to 100%), and mean hydroxychloroquine levels were significantly higher in patients with less disease activity. Cellular levels of patients on daily hydroxychloroquine have been shown to be higher in mononuclear cells than polymorphonuclear leucocytes.

Microbiology: ***Malaria:*** *Mechanism of Action:* The precise mechanism by which hydroxychloroquine exhibits activity against *Plasmodium* is not known. Hydroxychloroquine, like chloroquine, is a weak base and may exert its effect by concentrating in the acid vesicles of the parasite and by inhibiting polymerization of heme. It can also inhibit certain enzymes by its interaction with DNA.

Activity in vitro and in Clinical Infections: Hydroxychloroquine is active against the erythrocytic forms of chloroquine sensitive strains of *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium vivax.* Hydroxychloroquine is not active against the gametocytes and exoerythrocytic forms including the hypnozoite stage (*P. vivax* and *P. ovale*) of the *Plasmodium* parasites.

Drug Resistance: P. falciparum strains exhibiting reduced susceptibility to chloroquine also show reduced susceptibility to hydroxychloroquine.

Resistance of *Plasmodium* parasites to chloroquine is widespread (see INDICATIONS AND USAGE: Malaria).

Patients in whom chloroquine or hydroxychloroquine have failed to prevent or cure clinical malaria or parasitemia, or patients who acquired malaria in a geographic area where chloroquine resistance is known to occur should be treated with another form of antimalarial therapy (see INDICATIONS AND USAGE: Malaria and WARNINGS).

Rheumatoid Arthritis and Systemic Lupus Erythematosus: ***Mechanism of Action:*** The mechanisms underlying the anti-inflammatory and immunomodulatory effects of hydroxychloroquine sulfate tablets are unknown.

INDICATIONS AND USAGE: Malaria: Hydroxychloroquine sulfate tablets are indicated for the treatment of uncomplicated malaria due to *P. falciparum, P. malariae, P. ovale,* and *P. vivax.*

Hydroxychloroquine sulfate tablets are indicated for the prophylaxis of malaria in geographic areas where chloroquine resistance is not reported.

Limitations of Use in Malaria:

- Hydroxychloroquine sulfate tablets are not recommended for the treatment of complicated malaria.
- Hydroxychloroquine sulfate tablets are not effective against chloroquine or hydroxychloroquine-resistant strains of *Plasmodium* species (see CLINICAL PHARMACOLOGY: Microbiology). Hydroxychloroquine sulfate tablets are not recommended for the treatment of malaria acquired in geographic areas where chloroquine resistance occurs or when the *Plasmodium* species has not been identified.
- Hydroxychloroquine sulfate tablets are not recommended for malaria prophylaxis in geographic areas where chloroquine resistance occurs.
- Hydroxychloroquine sulfate tablets do not prevent relapses of *P. vivax* or *P. ovale* because it is not active against the hypnozoite forms of these parasites. For radical cure of *P. vivax* and *P. ovale* infections, concomitant therapy with an 8-aminoquinoline compound is necessary (see CLINICAL PHARMACOLOGY: Microbiology).

Prior to prescribing hydroxychloroquine sulfate tablets for the treatment or prophylaxis of malaria, consult the Centers for Disease Control and Prevention (CDC) Malaria website (http://www.cdc.gov/malaria).

Lupus Erythematosus: Hydroxychloroquine sulfate tablets are indicated for the treatment of chronic discoid lupus erythematosus and systemic lupus erythematosus in adults.

Rheumatoid Arthritis: Hydroxychloroquine sulfate tablets are indicated for the treatment of acute and chronic rheumatoid arthritis in adults.

CONTRAINDICATIONS: Use of hydroxychloroquine sulfate tablets are contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds.

WARNINGS: Resistant Strains of Malaria: Hydroxychloroquine sulfate tablets are not effective against chloroquine-resistant strains of *P. falciparum* (see CLINICAL PHARMACOLOGY: Microbiology).

Ocular: Irreversible retinal damage has been observed in some patients who had received hydroxychloroquine sulfate. Significant risk factors for retinal damage include daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years, subnormal glomerular filtration, use of some concomitant drug products such as tamoxifen citrate and concurrent macular disease.

A baseline ocular examination is recommended within the first year of starting hydroxychloroquine sulfate tablets. The baseline exam should include: best corrected distance visual acuity (BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted), and spectral domain ocular coherence tomography (SD-OCT).

For individuals with significant risk factors (daily dose of hydroxychloroquine sulfate greater than 5.0 mg/kg base of actual body weight, subnormal glomerular filtration, use of tamoxifen citrate or concurrent macular disease) monitoring should include annual examinations which include BCVA, VF and SD-OCT. For individuals without significant risk factors, annual exams can usually be deferred until five years of treatment.

In individuals of Asian descent, retinal toxicity may first be noticed outside the macula. In patients of Asian descent, it is recommended that visual field testing be performed in the central 24 degrees instead of the central 10 degrees.

It is recommended that hydroxychloroquine be discontinued if ocular toxicity is suspected and the patient should be closely observed given that retinal changes (and visual disturbances) may progress even after cessation of therapy.

Cardiac Effects, including Cardiomyopathy and QT Prolongation: Postmarketing cases of life-threatening and fatal cardiomyopathy have been reported with use of hydroxychloroquine sulfate tablets as well as with use of chloroquine. Patients may present with atrioventricular block, pulmonary hypertension, sick sinus syndrome or with cardiac complications. ECG findings may include atrioventricular, right or left bundle branch block. Signs or symptoms of cardiac compromise have appeared during acute and chronic treatment. Clinical monitoring for signs and symptoms of cardiomyopathy is advised, including use of appropriate diagnostic tools such as ECG to monitor patients for cardiomyopathy during hydroxychloroquine sulfate tablets therapy. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrio-ventricular heart block) or biventricular hypertrophy are diagnosed. If cardiotoxicity is suspected, prompt discontinuation of hydroxychloroquine sulfate tablets may prevent life-threatening complications.

Hydroxychloroquine sulfate tablets prolong the QT interval. Ventricular arrhythmias and torsades de pointes have been reported in patients taking hydroxychloroquine sulfate tablets (see OVERDOSAGE). Therefore, hydroxychloroquine sulfate tablets should not be administered with other drugs that have the potential to prolong the QT interval (see DRUG INTERACTIONS).

Worsening of Psoriasis and Porphyria: Use of hydroxychloroquine sulfate tablets in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. The preparation should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the possible hazard.

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, have been reported. Muscle and nerve biopsies have been associated with curvilinear bodies and muscle fiber atrophy with vacuolar changes. Assess muscle strength and deep tendon reflexes periodically in patients on long-term therapy with hydroxychloroquine sulfate tablets.

Neuropsychiatric Events, including Suicidality: Suicidal behavior has been rarely reported in patients treated with hydroxychloroquine sulfate tablets.

Hypoglycemia: Hydroxychloroquine sulfate tablets have been shown to cause severe hypoglycemia including loss of consciousness that could be life-threatening in patients treated with or without antidiabetic medications (see DRUG INTERACTIONS and ADVERSE REACTIONS). Patients treated with hydroxychloroquine sulfate tablets should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with hydroxychloroquine sulfate tablets should have their blood glucose checked and treatment reviewed as necessary.

PRECAUTIONS: General: Use with caution in patients with gastrointestinal, neurological, or blood disorders, and in those with a sensitivity to quinine.

Hepatic/Renal Disease: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. A reduction in dosage may be necessary in patients with hepatic or renal disease, as well as in those taking medicines known to affect these organs.

Hematologic Effects/Laboratory Tests: Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. Periodic blood cell counts should be performed if patients are given prolonged therapy. If any severe blood disorder such as aplastic anemia, agranulocytosis, leukopenia, or thrombocytopenia, appears which is not attributable to the disease under treatment, consider discontinuation of hydroxychloroquine sulfate tablets.

Hydroxychloroquine sulfate tablets should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Dermatologic Effects: Dermatologic reactions to hydroxychloroquine sulfate tablets may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

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

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

Drugs that Prolong QT Interval and Other Arrhythmogenic Drugs: Hydroxychloroquine sulfate tablets prolong the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine sulfate tablets are used concomitantly with other arrhythmogenic drugs.

Mefloquine and Other Drugs Known to Lower the Convulsive Threshold: Hydroxychloroquine sulfate tablets can lower the convulsive threshold. Co-administration of hydroxychloroquine sulfate tablets with other antimalarials known to lower the convulsion threshold (e.g., mefloquine) may increase the risk of convulsions.

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

Methotrexate: Combined use of methotrexate with hydroxychloroquine sulfate tablets have not been studied and may increase the incidence of adverse effects.

Cyclosporin: An increased plasma cyclosporin level was reported when cyclosporin and hydroxychloroquine sulfate tablets were co-administered.

The following interactions have been observed on treatment with the structurally related substance chloroquine phosphate, and therefore cannot be ruled out for hydroxychloroquine.

Praziquantel: Chloroquine has been reported to reduce the bioavailability of praziquantel.

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

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

Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin.

Information for Patients: Patients should be informed of the early signs and symptoms of toxicity such as rash or visual changes. Patients must see their physicians promptly in case of the appearance of these or of any unusual effects. Periodic laboratory tests may be recommended in some patients. Patients should be fully informed of the potential risks of the use of hydroxychloroquine sulfate tablets, especially in pregnancy and in children.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of hydroxychloroquine sulfate tablets.

The mutagenic potential of hydroxychloroquine was not evaluated. However, chloroquine has been shown to be a catalytic inhibitor of DNA repair enzymes (topoisomerase II) and to produce weak genotoxic effects through this mode of action.

Pregnancy: ***Teratogenic Effects:*** Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defects has been demonstrated. Embryonic deaths and malformations of anophthalmia and microphthalmia in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers: Caution should be exercised when administering hydroxychloroquine sulfate tablets to nursing women. It has been demonstrated that hydroxychloroquine administered to nursing women is excreted in human milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Pediatric Use: Safety and efficacy have not been established in the chronic use of hydroxychloroquine sulfate tablets for systemic lupus erythematosus and juvenile idiopathic arthritis in children. Children are especially sensitive to the 4-aminoquinoline compounds. Most reported fatalities followed the accidental ingestion of chloroquine, sometimes in small doses (0.75 g or 1 g in one 3-year-old child). Patients should be strongly warned to keep these drugs out of the reach of children (see OVERDOSAGE).

Geriatric Use: Clinical studies of hydroxychloroquine sulfate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, this 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. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

ADVERSE REACTIONS: The following adverse reactions have been identified during post-approval use of hydroxychloroquine sulfate tablets or other 4-aminoquinoline compounds. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Cardiac Disorders: Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see WARNINGS and OVERDOSAGE). Hydroxychloroquine sulfate tablets prolong the QT interval. Ventricular arrhythmias and torsade de pointes have been reported in patients taking hydroxychloroquine sulfate tablets (see OVERDOSAGE and DRUG INTERACTIONS).

Ear and Labyrinth Disorders: Vertigo, tinnitus, nystagmus, nerve deafness, deafness.

Eye Disorders: Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas) and visual disturbances (visual acuity), maculopathies (macular degeneration), decreased dark adaptation, color vision abnormalities, corneal changes (edema and opacities) including corneal deposition of drug with or without accompanying symptoms (halo around lights, photophobia, blurred vision).

Gastrointestinal Disorders: Nausea, vomiting, diarrhea, and abdominal pain.

General Disorders and Administration Site Conditions: Fatigue.

Hepatobiliary Disorders: Liver function tests abnormal, hepatic failure acute.

Immune System Disorders: Urticaria, angioedema, bronchospasm.

Metabolism and Nutrition Disorders: Decreased appetite, hypoglycemia, porphyria, weight decreased.

Musculoskeletal and Connective Tissue Disorders: Sensorimotor disorder, skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, depression of tendon reflexes and abnormal nerve conduction.

Nervous System Disorders: Headache, dizziness, seizure, ataxia and extrapyramidal disorders such as dystonia, dyskinesia, and tremor have been reported with this class of drugs.

Psychiatric Disorders: Affect/emotional lability, nervousness, irritability, nightmares, psychosis, suicidal behavior.

Skin and Subcutaneous Tissue Disorders: Rash, pruritus, pigmentation disorders in skin and mucous membranes, hair color changes, alopecia. Dermatitis bullous eruptions including erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), photosensitivity, dermatitis exfoliative, acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although hydroxychloroquine sulfate tablets may precipitate attacks of psoriasis. It may be associated with pyrexia and hyperleukocytosis.

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE: The 4-aminoquinoline compounds are very rapidly and completely absorbed after ingestion, and in accidental overdosage, or rarely with lower doses in hypersensitive patients, toxic symptoms may occur within 30 minutes. The symptoms of overdosage may include 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. Treatment is symptomatic and must be prompt. Immediate gastric lavage until the stomach is completely emptied is indicated. After lavage, activated charcoal is introduced by the stomach tube within 30 minutes of ingestion of the drug may inhibit further intestinal absorption. To be effective, the dose of activated charcoal should be at least five times the estimated dose of hydroxychloroquine ingested.

Consideration should be given to administering diazepam parenterally since studies suggest that it may be beneficial in reversing chloroquine and hydroxychloroquine cardiotoxicity.

Respiratory support and shock management should be instituted as necessary.

Exchange transfusions are used to reduce the level of 4-aminoquinoline drug in the blood.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least six hours. Fluids may be forced and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine. This will promote urinary excretion in cases of both overdosage and sensitivity. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

DOSAGE AND ADMINISTRATION: One hydroxychloroquine sulfate tablet contains 200 mg of hydroxychloroquine sulfate, which is equivalent to 155 mg base.

Take hydroxychloroquine sulfate tablets with a meal or a glass of milk.

Malaria: ***Prophylaxis:*** Adults: 400 mg (310 mg base) once weekly on the same day of each week starting 2 weeks prior to exposure, and continued for 4 weeks after leaving the endemic area.

Weight-Based Dosing in Adults and Pediatric Patients: 6.5 mg/kg (5 mg/kg base), not to exceed 400 mg (310 mg base), once weekly on the same day of the week starting 2 weeks prior to exposure, and continued for 4 weeks after leaving the endemic area.

Treatment of Uncomplicated Malaria: Adults: 800 mg (620 mg base) followed by 400 mg (310 mg base) at 6 hours, 24 hours and 48 hours after the initial dose (total 2000 mg hydroxychloroquine sulfate or 1550 mg base).

Weight Based Dosage in Adults and Pediatric Patients: 13 mg/kg (10 mg/kg base), not to exceed 800 mg (620 mg base) followed by 6.5 mg/kg (5 mg/kg base), not to exceed 400 mg (310 mg base), at 6 hours, 24 hours and 48 hours after the initial dose. Hydroxychloroquine sulfate tablets film-coated tablets cannot be divided, therefore they should not be used to treat patients who weigh less than 31 kg.

For radical cure of *P. vivax* and *P. malariae* infections, concomitant therapy with an 8-aminoquinoline compound is necessary.

Lupus Erythematosus: The recommended adult dosage is 200 mg to 400 mg (155 mg to 310 mg base) daily, administered as a single daily dose or in two divided doses. Doses above 400 mg a day are not recommended.

The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Rheumatoid Arthritis: The action of hydroxychloroquine is cumulative and may require weeks to months to achieve the maximum therapeutic effect (see CLINICAL PHARMACOLOGY).

Initial Adult Dosage: 400 mg to 600 mg (310 mg to 465 mg base) daily, administered as a single daily dose or in two divided doses. In a small percentage of patients, side effects may require temporary reduction of the initial dosage.

Maintenance Adult Dosage: When a good response is obtained, the dosage may be reduced by 50 percent and continued at a maintenance level of 200 mg to 400 mg (155 mg to 310 mg base) daily, administered as a single daily dose or in two divided doses.

Do not exceed 600 mg or 6.5 mg/kg (5 mg/kg base) per day, whichever is lower, as the incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Corticosteroids and salicylates may be used in conjunction with hydroxychloroquine sulfate tablets, and they can generally be decreased gradually in dosage or eliminated after a maintenance dose of hydroxychloroquine sulfate tablets has been achieved.

HOW SUPPLIED: Hydroxychloroquine Sulfate Tablets, USP are available containing 200 mg of hydroxychloroquine sulfate, USP, equivalent to 155 mg of base.

The 200 mg tablets are white, film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **373** on the other side. They are available as follows:

NDC 0378-0373-01
bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child resistant closure. Keep out of the reach of children.

Do not crush or divide hydroxychloroquine sulfate film-coated tablets (see DOSAGE AND ADMINISTRATION).

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Revised: 2/2017
HXCQ:R10

Appendix D: Exclusion Medication List

Digoxin	Praziquantel
Mefloquine	Antacids
Tamoxifen citrate	Kaolin
Methotrexate	Cimetidine
Cyclosporine	Ampicillin
Insulin	Laxatives
Antidiabetic drugs	Enemas
Loop diuretics	Amphotericin B
Thiazides	High dose corticosteroids
Pyridostigmine	Proton pump inhibitors
	Neostigmine
	Pyridostigmine

CredibleMeds Filtered QTDrug List

The last revision date: March 19, 2020

See Note below for safe use of this Table
The drug list below contains drugs from the categories: Known Risk of TdP, Possible Risk of TdP AND filtered by
Market filter: Only Drugs on US Market AND filtered by Keyword --> " "

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Alfuzosin	Uroxatral	Alpha-1 adrenergic blocker	Benign prostatic hyperplasia	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia	Risk of TdPAnd Avoid in congenital long QT	oral
Apalutamide	Erleada	Nonsteroidal antiandrogen	Cancer (prostate)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Dopamine agonist	Parkinson's disease	Possible Risk of TdPAnd Avoid in congenital long QT	oral, sublingual, injection
Aripiprazole	Abilify, Aripiprex	Antipsychotic, atypical	Schizophrenia, depression (adjunct)	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)	Risk of TdPAnd Avoid in congenital long QT	injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Artemether/Lumefantrin e	Coartem	Anti-malarial	Marlaria	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Asenapine	Saphris, Sycrest	Antipsychotic, atypical	Schizophrenia	Possible Risk of TdPAnd Avoid in congenital long QT	sublingual
Atomoxetine	Strattera	CNS stimulant	ADHD	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Bedaquiline	Sirturo	Antibiotic	Tuberculosis, Multi-drug resistant	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Bendamustine	Treanda, Treakisym, Ribomustin, Levact	Anti-cancer	Cancer (Leukemia, lymphoma)	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)	Risk of TdPAnd Avoid in congenital long QT	oral
Betrixaban	Bevyxxa	Anticoagulant	Anticoagulant	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Bortezomib	Velcade, Bortecad	Proteasome inhibitor	Cancer (multiple myeloma, lymphoma)	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Bosutinib	Bosulif	Anti-cancer	Cancer (leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Buprenorphine	Butrans, Belbuca, Bunavail, Buprenex, Subutex, Suboxone, Zubsolv	Opioid agonist	Narcotic addiction and pain	Possible Risk of TdPAnd Avoid in congenital long QT	sublingual, topical, injection
Cabozantinib	Cometriq	Anti-cancer	Cancer (renal cell)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Capecitabine	Xeloda	Anti-cancer	Cancer (GI, Breast)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Ceritinib	Zykadia	Anti-cancer	Cancer (Lung)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Cesium Chloride	Energy Catalyst	Toxin	Alternative therapy cancer	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Chloroquine	Aralen	Antimalarial	Malaria	Risk of TdPAnd Avoid in congenital long QT	oral
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Nausea, Schizophrenia, many others	Risk of TdPAnd Avoid in congenital long QT	oral, injection, suppository
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittentcl	Risk of TdPAnd Avoid in congenital long QT	oral
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression	Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection	Risk of TdPAnd Avoid in congenital long QT	oral, inhaled
Clozapine	Clozaril, Fazaclo, Versacloz	Antipsychotic, atypical	Schizophrenia	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Cobimetinib	Cotellic	Anti-cancer	Cancer (Melanoma)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Crizotinib	Xalkori	Anti-cancer	Cancer (Non-small cell lung cancer, metastatic)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Dabrafenib	Tafinlar	Anti-cancer	Cancer (melanoma)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Dasatinib	Sprycel	Anti-cancer	Cancer (leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Degarelix	Firmagon, Ferring	Anti-androgen	Cancer (prostate)	Possible Risk of TdPAnd Avoid in congenital long QT	injection, suppository
Desipramine	Pertofrane, Norpramine	Antidepressant, Tricyclic	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Deutetrabenazine	Austedo	Vesicular monamine transporter 2 inhibitor	Chorea (Huntington's disease)	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Dextromethorphan/Quinidine	Nuedexta	Unknown	Pseudobulbar affect	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral
Dolasetron	Anzemet	Antiemetic	Nausea, vomiting	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	Risk of TdPAnd Avoid in congenital long QT	oral
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral
Efavirenz	Sustiva	Antiviral	HIV/AIDS	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Eliglustat	Cerdelga	Glucosylceramide synthase inhibitor	Gaucher's disease	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Encorafenib	Braftovi	BRAF inhibitor	Cancer (Melanoma)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Entrectinib	Rozlytrek	Anti-cancer	Cancer (Lung)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Epirubicin	Ellence, Pharmorubicin, Epirubicin Ebewe	Anti-cancer	Cancer	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Eribulin mesylate	Halaven	Anti-cancer	Cancer (breast, metastatic)	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI	Depression (major), anxiety disorders	Risk of TdPAnd Avoid in congenital long QT	oral
Ezogabine (Retigabine)	Potiga, Trobalt	Anticonvulsant	Seizures, Partial	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Felbamate	Felbatol	Anticonvulsant	Seizures	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Fingolimod	Gilenya	Sphingosine phospate receptor modulator	Multiple Sclerosis	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Fluorouracil (5-FU)	Adrucil, Carac, Efudex, Efudix	Anti-cancer	Cancer	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Gemifloxacin	Factive	Antibiotic	Bacterial infection	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Gilteritinib	Xospata	Antineoplastic	Cancer (Acute Myeloid Leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Glasdegib	Daurismo	Anti-cancer	Cancer (Acute myeloid leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Granisetron	Kytril, Sancuso, Granisol	Antiemetic	Nausea, vomiting	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection, topical
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation	Risk of TdPAnd Avoid in congenital long QT	oral, injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Hydrocodone - ER	Hysingla™ ER, Zohydro ER	Analgesic	Pain, severe	Possible Risk of TdPAnd Avoid in congenital long QT	oral, suppository
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis	Risk of TdPAnd Avoid in congenital long QT	oral
Iloperidone	Fanapt, Fanapta, Zomaril	Antipsychotic, atypical	Schizophrenia	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Imipramine (Melipramine)	Tofranil	Antidepressant, Tricyclic	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Inotuzumab ozogamicin	Besponsa	Anti-cancer	Cancer (acute lymphocytic leukemia}	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Isradipine	Dynacirc	Antihypertensive	Hypertension	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Ivosidenib	Tibsovo	IDH1 inhibitor	Cancer (Acute myeloid leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Lapatinib	Tykerb, Tyverb	Anti-cancer	Cancer (breast, metastatic)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Lefamulin	Xenleta	Antibiotic	Community acquired pneumonia	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Lenvatinib	Lenvima	Anti-cancer	Cancer (Thyroid)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Leuprolide (Leuprorelin)	Lupron, Eligard, Viadur, Carcinil, Enanton, Leuplin, Lucrin, Procren, Prostap	Anti-androgen	Cancer (prostate)	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Lithium	Eskalith, Lithobid	Antimanic	Bipolar disorder	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Lofexidine	Lucemyra	Alpha-2-adrenergic agonist, central	Opioid withdrawal syndrome	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Lopinavir/Ritonavir	Kaletra, Aluvia	Antiviral	HIV/AIDS	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Lumateperone	Caplyta	Antipsychotic, atypical	Schizophrenia	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Lurasidone	Latuda	Antipsychotic, atypical	Schizophrenia, biopolar disorder and others	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Maprotiline	Ludiomil	Anti-depressant, Tetracyclic	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Memantine	Namenda XR	NMDA receptor antagonist	Alzheimer's disease	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Midostaurin	Rydapt	Anti-cancer	Cancer (Acute myeloid leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Mifepristone	Korlym, Mifeprex	Progesterone antagonist	Pregnancy termination	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Mirabegron	Myrbetriq	Beta3 adrenergic antagonist	Bladder spasm	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Mirtazapine	Remeron	Antidepressant, Tetracyclic	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Moexipril/Hydrochlorothiazide	Uniretic, Univasc	Antihypertensive	Hypertension, diuresis	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Necitumumab	Portrazza	Anti-cancer	Cancer (Lung)	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Nicardipine	Cardene	Antihypertensive	Hypertension	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Nilotinib	Tasigna	Anti-cancer	Cancer (leukemia)	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Nortriptyline	Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen	Antidepressant, Tricyclic	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Nusinersen	Spinraza	Antisense oligonucleotide	Spinal Muscular Atrophy	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Ofloxacin	Floxin	Antibiotic	Bacterial infection	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting	Risk of TdPAnd Avoid in congenital long QT	oral, injection, suppository
Osimertinib	Tagrisso	Anti-cancer	Cancer (EGFR pos. NSC Lung cancer)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Oxaliplatin	Eloxatin	Anti-cancer	Cancer	Risk of TdPAnd Avoid in congenital long QT	injection
Paliperidone	Invega, Xepilon	Antipsychotic, atypical	Schizophrenia	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Palonosetron	Aloxi	Antiemetic	Nausea, vomiting	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Panobinostat	Farydak	Histone deacetylase inhibitor	Cancer, Multiple myeloma	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Pasireotide	Signifor	Somatostatin analog	Cushings Disease	Possible Risk of TdPAnd Avoid in congenital long QT	injection, topical
Pazopanib	Votrient	Anti-cancer	Cancer (renal cell, sarcoma)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)	Risk of TdPAnd Avoid in congenital long QT	injection, inhaled
Perphenazine	Trilafon, Etrafon/Triavil, Decentan	Antipsychotic	Schizophrenia	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Pimavanserin	Nuplazid	Antipsychotic, atypical	Psychosis, Parkinson's Disease	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Pimozide	Orap	Antipsychotic	Tourette's Disorder	Risk of TdPAnd Avoid in congenital long QT	oral
Pitolisant (Tiprolisant)	Wakix	Histamine 3 antagonist/inverse agonist	Narcolepsy	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Pretomanid		Antitubercular	Tuberculosis, extensively drug resistant	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Primaquine phosphate		Antimalarial	Malaria	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	injection
Promethazine	Phenergan	Antipsychotic / Antiemetic	Nausea, vomiting	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection, suppository
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral, injection
Ribociclib	Kisqali	Anti-cancer	Cancer (breast)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Rilpivirine	Edurant, Complera, Eviplera, Juluca	Antiviral	Viral infection (HIV/AIDS)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Romidepsin	Istodax	Histone deacetylase inhibitor	Cancer (lymphoma)	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Saquinavir	Invirase(combo)	Antiviral	Viral infection (HIV/AIDS)	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Siponimod	Mayzent		Multiple Sclerosis	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Sorafenib	Nexavar	Anti-cancer	Cancer (liver, renal cell, metastatic thyroid)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Arrhythmia	Risk of TdPAnd Avoid in congenital long QT	oral
Sunitinib	Sutent	Anti-cancer	Cancer (GIST, renal cell, pNET)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Tacrolimus	Prograf, Prograf, Advagraf, Protopic	Immunosuppressant	Immune suppression	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Tamoxifen	Nolvadex, Istubal	Anti-cancer	Cancer (breast)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Tazemetostat	Tazverik	Anti-cancer	Epithelioid sarcoma	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Telavancin	Vibativ	Antibiotic	Bacterial infection	Possible Risk of TdPAnd Avoid in congenital long QT	injection
Tetrabenazine	Nitoman, Xenazine	Vesicular Monoamine Transporter 2 Inhibitor	Chorea (Huntington's disease)	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia	Risk of TdPAnd Avoid in congenital long QT	oral
Tipiracil/Trifluridine	Lonsurf	Anti-cancer	Cancer (Metastatic colorectal)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Tizanidine	Zanaflex, Sirdalud	Muscle relaxant	Muscle spasticity	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Tolterodine	Detrol, Detrusitol	Muscle relaxant	Bladder spasm	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Toremifene	Fareston	Estrogen agonist/antagonist	Cancer (breast, metastatic)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Tramadol	Crispin, Ralivia ER, Ralivia Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol, Ixprim, Zaldiar, Topalgic	Analgesic	Pain	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection, suppository
Trimipramine	Surmontil, Rhotrimine, Stangyl	Antidepressant, Tricyclic	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection
Valbenazine	Ingrezza	Vesicular monamine transporter 2 inhibitor	Tardive Dyskinesia	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)	Risk of TdPAnd Avoid in congenital long QT	oral
Vardenafil	Levitra	Phosphodiesterase 5 inhibitor	Erectile dysfunction	Possible Risk of TdPAnd Avoid in congenital long QT	oral, injection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Vemurafenib	Zelboraf	Anti-cancer	Cancer (melanoma)	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Venlafaxine	Effexor, Efexor	Antidepressant, SNRI	Depression	Possible Risk of TdPAnd Avoid in congenital long QT	oral
Vorinostat	Zolinza	Histone deacetylase inhibitor	Cancer (lymphoma)	Possible Risk of TdPAnd Avoid in congenital long QT	oral

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form.

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Appendix E: References

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