

Hydroxychloroquine (Plaquenil)| MOA, Uses, Side effects, and Dosage

Hydroxychloroquine is a synthetic antimalarial agent derived from chloroquine. While it retains activity against *Plasmodium* species, it is more commonly used for autoimmune diseases due to its **anti-inflammatory and immunomodulatory effects** .

Indications

FDA-Approved Uses

- **Malaria** : Treatment and prophylaxis of *Plasmodium vivax* , *P. ovale* , *P. malariae* , and *chloroquine-sensitive P. falciparum* .
- **Systemic Lupus Erythematosus (SLE)** : Reduces skin lesions, fatigue, joint pain, and prevents disease flares.
- **Rheumatoid Arthritis (RA)** : DMARD used to control inflammation and prevent joint damage.
- **Porphyria Cutanea Tarda**

Off-Label Uses

- **Juvenile Idiopathic Arthritis**
- **Primary Sjögren's Syndrome**

Hydroxychloroquine and COVID-19: Summary of Evidence

- Early in the COVID-19 pandemic, hydroxychloroquine was proposed as a potential treatment due to its *in vitro* antiviral activity against SARS-CoV-2.
- **Mechanism hypothesized:**
 - Interfered with endosomal pH needed for viral entry and replication.
 - Inhibited binding of viral spike protein to ACE2 receptors.
- **2020 Recovery Trial (UK)** and other RCTs found no clinical benefit.
- **FDA revoked Emergency Use Authorization (EUA)** in June 2020 due to lack of efficacy and risk of QT prolongation and cardiac arrhythmias.

Key Point: Hydroxychloroquine is *not* recommended for the prevention or treatment of COVID-19.

Mechanism of Action

Hydroxychloroquine has **multiple mechanisms** depending on the condition treated:

In Autoimmune Disorders:

- Increases **lysosomal pH** in antigen-presenting cells ? impairs antigen processing and presentation.
- Inhibits **toll-like receptors (TLR 7 and TLR 9)** on plasmacytoid dendritic cells ? ? interferon release.
- Reduces neutrophil chemotaxis and eosinophil activity.
- Suppresses **autoantigen presentation** , dampening immune activation.

In Malaria:

- Prevents the **biocrystallization of heme into hemozoin** in the parasite's food vacuole.
- Accumulation of free heme is **toxic** to the parasite ? lysis and death.

Pharmacokinetics

Parameter	Details
Absorption	Rapid and complete GI absorption
Bioavailability	~67–74%
Peak Plasma Time	1–3 hours
Protein Binding	~55%
Metabolism	Hepatic (CYP2D6, 2C8, 3A4/5) ? N-desethylhydroxychloroquine
Excretion	Renal (partially unchanged); long half-life (40–50 days)

Pharmacodynamics

- Lipophilic weak base ? accumulates in lysosomes.
- Increases lysosomal pH ? disrupts protein degradation and immune signaling.
- Alters MHC class II antigen processing.
- Inhibits intracellular pathways related to immune activation.

Onset and Duration

- **Onset of Action** : Typically 4–6 weeks; may take up to 6 months for full effect in autoimmune diseases.
- **Duration of Action** : Prolonged due to tissue accumulation (esp. skin, retina).

Therapeutic Benefits in Autoimmune Diseases

Hydroxychloroquine is considered **first-line therapy in SLE** due to:

- **Antithrombotic properties** : Decreases lupus-associated thrombosis.
- **Glycemic control** : Improves insulin sensitivity.
- **Lipid profile improvement** : ? LDL and triglycerides.
- ? Disease flares and long-term organ damage.

Adverse Effects

System	Adverse Effect
Ocular	Retinopathy (dose-dependent; screen annually)
Cardiac	QT prolongation, cardiomyopathy (rare but serious)
GI	Nausea, diarrhea, abdominal pain
Dermatologic	Hyperpigmentation, rash
Hematologic	Bone marrow suppression (rare)
CNS	Headache, dizziness

Retinopathy risk increases with daily doses >5 mg/kg of actual body weight and long-term use (>5 years).

Contraindications

- Hypersensitivity to 4-aminoquinoline compounds
- Retinal or visual field changes
- Pre-existing maculopathy

Monitoring Parameters

- **Ophthalmologic exam** : Baseline + annually after 5 years of use (or earlier if risk factors)
- CBC and LFTs if long-term use
- Baseline ECG if other QT-prolonging drugs are used