APRIL 2023

COMPOUNDING SAFETY INFORMATION

QUINACRINE HYDROCHLORIDE

On April 6, 2023, the Food and Drug Administration (FDA) added quinacrine hydrochloride (HCl), for oral use only, to the list of bulk drug substances that can be used by outsourcing facilities to compound drug products under section 503B of the Federal Food, Drug and Cosmetics Act (FD&C Act). FDA's review for the 503B Bulks List determined that there is a clinical need for drug products compounded from the bulk drug substance quinacrine HCl in the treatment of some patients with cutaneous lupus erythematosus.[1]

The safety information below describes known risks and potential adverse effects related to the use of quinacrine HCl drug products for oral administration. Although quinacrine HCl may be used to compound oral drug products under section 503B of the FD&C Act, compounded drugs such as quinacrine HCl are not reviewed and approved by FDA for safety, effectiveness, or quality.

The information below is based on a limited review of available scientific literature regarding known safety risks associated with the oral use of quinacrine HCl and is not a comprehensive list of all potential adverse effects related to use of quinacrine HCl drug products. FDA's consideration of this substance for use under section 503B was necessarily far more limited than FDA's review of an application for approval of a new drug application under the statutory standard in section 505 of the FD&C Act. In addition to adverse events associated with the oral use of quinacrine HCl, substandard product quality and/or particular attributes of the drug product formulation may also cause adverse events. FDA encourages providers and patients to report adverse events to MedWatch.

KNOWN SAFETY RISKS

Quinacrine HCl may not be compounded for intrauterine administration, such as for the purpose of non-surgical female sterilization.[2] Such drug products present serious safety risks and are not eligible for the exemptions under section 503B of the FD&C Act.

[1] See https://federalregister.gov/d/2023-07237 for the *Federal Register* Notice adding quinacrine HCl for oral use only to the 503B Bulks List. See: https://www.govinfo.gov/content/pkg/FR-2021-03-24/pdf/2021-06060.pdf for the Federal Register Notice describing FDA's consideration of quinacrine HCl for the 503B Bulks List.

[2] See http://web.archive.org/web/20190213203913if_/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM486146.pdf (pages 52-56) for the Background Package that FDA prepared for the March 8-9, 2016 meeting of the Pharmacy Compounding Advisory Committee (PCAC). More information about the PCAC meeting can be found at http://web.archive.org/web/20190207175049/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm486094.htm.

1. Hypersensitivities

Quinacrine HCl should not be used in those with known hypersensitivities to acridine dyes and derivatives.

2. Aplastic Anemia

Aplastic anemia is a rare occurrence in which bone marrow is unable to generate blood cells. In this condition, hemopoietic stem cells in bone marrow are destroyed and replaced by fat cells, reducing blood cell production (Young 2013). Quinacrine HCl may cause aplastic anemia (DeLoughery 1998; Lubran 1989). A report from World War II indicated that the rate of aplastic anemia among soldiers increased from 0.66 per 100,000 to 2.84 per 100,000 after the introduction of quinacrine HCl, which was used for treatment of malaria. The report also noted that a lichen planus rash developed before aplastic anemia in 50% of the cases (Custer 1946). In addition to performing routine observations of the skin for signs of the lichen planus rash, blood tests should be performed to monitor blood cell count.

3. Hemolytic Anemia Risk for Individuals with G-6-PD Deficiency

Quinacrine HCl should be avoided in those with known glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The enzyme G-6-PD maintains the function and integrity of red blood cells. A deficiency in this enzyme would result in reduced red blood cell stability and increased susceptibility to destruction by fever or by certain exogenous compounds (Howes et al. 2013). Use of quinacrine HCl in those with G-6-PD deficiency may destroy red blood cells and precipitate hemolytic anemia (Mason et al. 2007). Blood tests should be performed to determine red blood cell concentrations when evaluating a patient for hemolytic anemia.

4. Neurologic and Psychiatric Effects

Quinacrine HCl is associated with various severe reactions including convulsions, seizures, bipolar-like symptoms, and psychosis (Lally et al. 2012; Rockwell 1968; Weisholtz et al. 1982). A large study of more than 7,000 U.S. soldiers in World War II found the incidence of quinacrine HCl-induced psychosis to be 0.4% (Wallace 1989).

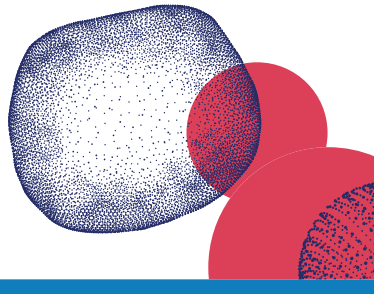
5. Hepatic Injury

Therapeutic doses of quinacrine HCl may increase plasma concentrations of liver function enzymes and are associated with rare occurrences of hepatitis (Collinge et al. 2009; Eshleman et al. 1970; Geschwind et al. 2013; Gibb et al. 1985; Namas and Marquardt 2015; Scoazec et al. 2003). Liver function tests should be conducted to monitor for signs of liver damage.

6. Dermatologic Effects

Quinacrine HCl's dermatologic effects are well documented.

- Yellowing of the skin, mucosa, and sclera may occur in those taking quinacrine HCl, often occurring within the initial weeks of treatment. The condition is asymptomatic and self-resolves after the drug is stopped or dose reduced (Vidal et al. 2013; Wallace 1989).
- Rashes, such as the lichen planus rash, developed in 2,000 out of 120,000 soldiers taking quinacrine HCl during World War II (Bauer 1981; Sehgal et al. 2011). As discussed above, lichen planus may develop as an initial sign of aplastic anemia.
- Hyperpigmentation has been associated with quinacrine HCl use and can present as black and blue sores or as oral discoloration. Hyperpigmentation resolves after discontinuation or dose reduction (Kleinegger et al. 2000).



KNOWN DRUG INTERACTIONS

1. Cytochrome P450E (CYP) 3A4/5 inhibitors: Quinacrine HCl is a CYP3A4/5 substrate; therefore, inhibitors of CYP3A4/5 may enhance its toxicities. Conversely, inducers of CYP3A4/5 may reduce quinacrine HCl's effectiveness (Huang et al. 2006).

2. CYP 2E1 substrates: Quinacrine HCl inhibits CYP2E1. Monitoring should be conducted when quinacrine HCl is used in conjunction with substrates of this enzyme (Karamanakos et al. 2009).

AVAILABLE INFORMATION REGARDING USE IN SPECIFIC POPULATIONS

1. Pregnancy

Pregnancy Exposure Registry: No pregnancy exposure registry exists for quinacrine HCl.

Risk Summary: Quinacrine HCl crosses the placenta, but fetal risk is unclear since there are no human data evaluating the safety of quinacrine in pregnancy (Louis 1996). An animal study evaluating intrauterine administration of quinacrine demonstrated an increase in the risk of fetal death; however, the study predates current standards for assessments of reproductive safety (Blake et al. 1983).

Clinical Considerations

Human Data

No human data exists regarding the use of quinacrine HCl in pregnant women.

Animal Data

Administration of quinacrine HCl dosed at 0.4 mg and 4 mg in a study of 170 rats on gestation day 8 and 12 demonstrated a significant, dose-dependent increase in the risk of fetal mortality versus placebo. Quinacrine HCl was administered into one uterine horn of a pregnant rat, while a placebo buffer solution was administered in the other. The horn receiving the 0.4 mg dose of quinacrine on gestation day 8 was associated with a fetus resorption rate of 31.2%, while the other horn had a fetus resorption rate of 18.4% ($p < 0.05$). The 4 mg dose administered on gestation day 8 was associated with a 51.8% rate of fetus resorption versus the 18.4% rate of resorption in the control horns ($p < 0.001$). Rat uterine horns administered 0.4 mg of quinacrine HCl on day 12 of gestation did not demonstrate a significant difference in fetal resorption versus horns that received placebo. However, the 4 mg dose of quinacrine administered on day 12 was associated with a 65.5% rate of fetal resorption versus the 27.6% rate of resorption in the horn that received placebo ($p < 0.001$) (Blake et al. 1983).

2. Lactation

Risk Summary: There are no data to assess the presence or absence of quinacrine HCl in human milk. Furthermore, there is no information on quinacrine HCl's effect on lactation.

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