Regulatory History and Safety of Quinacrine HCl

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Abstract

This presentation summarizes the regulatory history of quinacrine hydrochloride (HCl) for pharmaceutical compounding under Section 503A and 503B. Quinacrine HCl is an unapproved drug historically used in the treatment of malaria. It was nominated for the 503A Bulks List, established under Section 503A of the Food Drug and Cosmetic Act (FD&C Act), for pharmaceutical compounding. Bulk drug substances added to this list may be used to compound drug products by a licensed pharmacist or a physician at Section 503A compounding facilities. While there is supportive evidence for its effectiveness in treating patients with cutaneous lupus erythematosus, quinacrine HCl also poses significant safety risks. FDA proposed quinacrine HCl for the 503B Bulks List and also proposed to make safety information available to the prescribers, pharmacists and patients. This presentation summarizes the regulatory history of quinacrine as it relates to its evaluation under 503A and 503B, reviews published literature regarding its safety, in addition to compiling safety data designed to convey relevant risks to public stakeholders.

Introduction

Section 503A of Food Drug and Cosmetic Act

Under section 503A of the FD&C Act, drug products may be compounded from a bulk drug if the active pharmaceutical ingredient is a component of an FDA approved drug, is the subject of an applicable US Pharmacopeia or National Formulary drug monograph or appears on an FDA-generated list (the 503A Bulks List) of drug substances. Bulk drug substances (active pharmaceutical ingredients) are nominated for addition to the 503A Bulks list by the public or by FDA. If a nomination provides sufficient information for evaluation, a bulk drug substance is evaluated by the FDA for physical and chemical characterization, safety, effectiveness, and historical and current use in compounding.

Section 503B of Food Drug and Cosmetic Act

Section 503B of the FD&C Act, established in 2013 by the Drug Quality and Security Act, created a new category of compounders known as outsourcing facilities. Unlike compounders operating under section 503A, outsourcing facilities are subject to current good manufacturing process requirements, and they may distribute compounded drugs either pursuant to a patient-specific prescription or in response to an order from a health care provider, such as a hospital, that is not for an identified individual patient. Only substances on the FDA drug shortage list or on a list of bulk drug substances for which there is a clinical need, also known as the 503B Bulks List, may be compounded under section 503B. Public and FDA nominations for substances to the 503B Bulks List are evaluated by the FDA to assess and determine clinical need.

Nomination of Quinacrine HCl

Quinacrine HCl was nominated by a compounding pharmacy and pharmacy organizations for inclusion for the 503A Bulks List for the treatment of rheumatoid arthritis, lupus, as an antimalarial and an antiprotozoal, and for non-surgical female sterilization. The FDA later nominated quinacrine HCl to the 503B Bulks List for the treatment of cutaneous lupus erythematosus (CLE).

Materials and Methods

Mapping of the Regulatory History of Quinacrine HCl

The following sources of information were searched and reviewed for discussion related to quinacrine HCl:

- The Federal Register
- Documents and minutes from the 2016 Meeting Materials for the Pharmacy Compounding Advisory Committee (PCAC) meetings
- Regulations.gov

Composition of the Quinacrine HCl Safety Guide

Significant safety concerns mentioned in the Federal Register documents, PCAC meeting transcripts, and regulations.gov were identified. A literature search was performed to find all information pertaining to the safety concerns using the following resources: PubMed, National Toxicology Program website, Embase, Web of Science, PubChem Hazardous Substance Data Bank, NIH dietary supplement label database, Google, GRAS notice inventory, US Pharmacopeia, and Drugs@FDA.

Results and Discussion

Regulatory History

A summary memorandum published by the Office of New Drugs(OND) (included in the March 2016 PCAC briefing materials) recommended against adding quinacrine HCl to the 503A Bulks List because of serious adverse drug reactions (ADRs) and concerns regarding the fact that safety labeling would not be required for compounded quinacrine HCL under section 503A. OND recommended that quinacrine HCl should be made available through an expanded investigational new drug (IND) application, which would provide additional opportunities for the communication of safety information.
The March 2016 PCAC meeting briefing document contains evaluations of quinacrine HCl from three OND review divisions and their recommendations to the PCAC on the 503A Bulks List. The recommendations, explanations, and PCAC committee vote are listed in Table 1. FDA has not yet reached a final decision regarding the inclusion of quinacrine on the 503A Bulks List.

On March 24, 2021, the FDA published in the Federal Register (86 Fed. Reg. 15673) that no IND application has been submitted for quinacrine HCl. Additionally, it stated that the IND process would not be a realistic option to make quinacrine HCl available to patients with CLE. The FDA proposed to add quinacrine HCl, in oral dosage forms to the 503B Bulks List because it meets a clinical need for patients with CLE. Quinacrine HCl was described to be well-characterized both physically and chemically, has a long history of use in compounding, in addition to a significant body of literature demonstrating its potential effectiveness for the treatment of patients with CLE.

Figure 1. Summary of history of quinacrine HCl.

Results and Discussion

FDA Division or Committee	503A Bulks List Recommendation	Explanation
DAIP[1]	Not Recommended	DAIP reviewed quinacrine HCl's use as an antimicrobial and found that it might be effective for treatment of refractory giardiasis. However, little evidence is available to support this indication. DAIP stated that safety concerns outweigh any potential benefit for treatment of infectious disease.
DRTM[2]	Recommended	DRTM found that quinacrine fulfilled a therapeutic need in the treatment of CLE. They argued that severe adverse reactions could be managed by appropriate monitoring and dosing.
DUOG[3]	Not Recommended for Intrauterine Route of Administration	DUOG reviewed intrauterine use for non-surgical female sterilization. Quinacrine HCl is not as effective as other therapies in preventing births and presented concerns of mutagenicity, cytotoxicity and possible carcinogenicity.
FDA Overall Recommendation	Not Recommended	FDA did not recommend quinacrine for the 503A bulks list because of the serious adverse effects associated with its use and lack of an FDA approved drug label to guide safe and effective use.
PCAC Committee	Not Recommended	The PCAC Committee voted 6 to 5 against adding quinacrine HCl to the 503A Bulks List.

[1]Division of Anti-Infective Products
[2]Division of Rheumatology and Transplant Medicine, previously known as the Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
[3]Division of Urology, Obstetrics and Gynecology, previously known as the Division of Bone, Reproductive and Urologic Products (DBRUP)

Table 1. Summary of recommendations by FDA Divisions and PCAC Committee for the inclusion of quinacrine HCl to the 503A Bulks List in the 2016 PCAC meeting.

Safety Concerns Identified with Quinacrine HCl

In the March 24, 2021 Federal Register proposal to add quinacrine HCl to the 503B Bulks List, it stated that "FDA intends to make safety information about the use of quinacrine available to prescribers, pharmacists, outsourcing facilities, and the public through information on FDA's website, in a safety guide, or through other mechanisms, as appropriate. (86 Fed. Reg. 15673 @15677)". The March 2016 PCAC briefing document and presentation transcript identified the following severe reactions associated with use of quinacrine HCl: aplastic anemia, hemolytic anemia, precipitations of psychotic episodes, and rare instances of hepatic injury. Other side effects include yellowing of the skin, elevation of liver function enzymes, insomnia, irritability, restlessness, and general gastrointestinal symptoms. A dendrogram of published reports of adverse reactions to quinacrine HCl can be seen in Figure 2.

The literature search for ADRs related to quinacrine yielded 607 articles. A careful review of the titles and abstracts of the articles yielded 176 articles as relevant supporting information for ADRs to quinacrine. Relevant information included any article containing data pertaining to a toxicity or ADR associated with the use of quinacrine HCl. Animal models showed reproductive toxicity findings associated with quinacrine; however, limited clinical data exist on quinacrine's effects on pregnancy and lactation. Overall, quinacrine HCl presents safety concerns which may be conveyed to stakeholders and the public through publication of the safety guide or through other mechanisms.

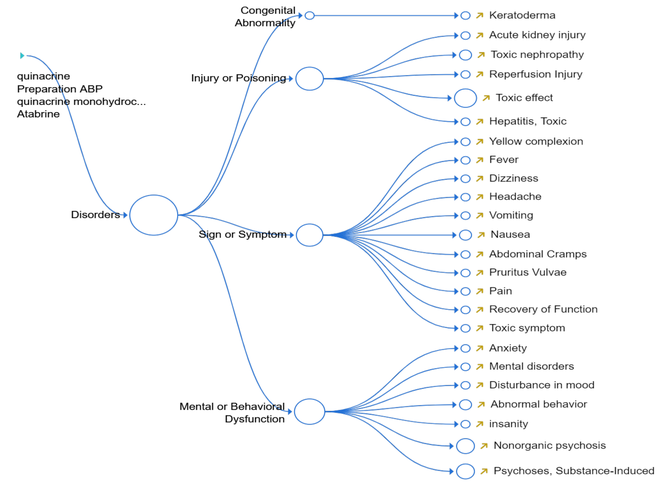

Figure 2. Dendrogram of search results exported from www.med.causaly.com. Dendrogram is depicting published adverse reactions associated with quinacrine HCl. All data from this search was sourced from Medline and PubMed Central.

Conclusion

Quinacrine HCl's regulatory history provides insight into the complex decision making involved in reviewing bulk drug substances for use in compounding. While clearly presenting safety risks, quinacrine HCl may offer therapeutic benefit for some patients with CLE. FDA proposes adding quinacrine HCl to the 503B Bulks List for oral use only. Furthermore, the proposed publication of a safety information on FDA's website, in a safety guide, or through other mechanisms would empower the public and other stakeholders by providing education on the risks associated with the use of quinacrine HCl.

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