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APPLICATION NUMBER:

21-078 / S-004

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-078
Generic	Atovaquone and proguanil hydrochloride
(Brand®)	Malarone
Submission Date:	January 11, 2002
Sponsor:	GlaxoSmithKline
Type of Submission:	Phase IV CMC Commitment-Dissolution Method for Atovaquone
Reviewer:	Houda Mahayni

Submission

The information contained in this supplement is as follows:

- Updated regulatory specifications for Malarone Tablets and Malarone Pediatric Tablets incorporating the atovaquone dissolution test and acceptance criteria.
- Analytical method and supporting validation for atovaquone dissolution in Malarone Tablets and Malarone Pediatric Tablets.

Study Design

In the original NDA (NDA 21-078), the dissolution test for the atovaquone component of Malarone Tablets and Malarone Pediatric Tablets utilized the USP type IV dissolution apparatus with [redacted]

The method filed in that submission had a sampling time of 1 hour and 45 minutes. However, the first hour of this dissolution method was water which was required to remove the proguanil hydrochloride from the tablet matrix before the atovaquone could be dissolved.

To eliminate the harsh testing conditions as recommended by the Agency, the sponsor developed another dissolution test method using the USP type II dissolution apparatus with a 40% isopropanol media buffered to pH 8.0 with potassium dihydrogen phosphate. The alcoholic media dissolves atovaquone to a suitable level while maintaining sink conditions in a type II apparatus.

The dissolution conditions for Malarone Tablets and Malarone Pediatric Tablets are provided below.

Apparatus:	USP type II with [redacted]
Medium:	900 mL of 40% isopropanol buffered to pH 8.0 with potassium dihydrogen phosphate
Stirring Speed:	50 rpm
Temperature:	37° C

Results

Atovaquone dissolution profiles for three production-scale batches each of Malarone Tablets and Malarone Pediatric Tablets of varying age are presented in Tables C1-C2 and Figures C1-C2, respectively. Sampling timepoints are different between the batches because the batches were tested at different times during development of the dissolution method.

Based on results of the production batches, a dissolution specification for atovaquone of Q = [redacted] at 45 minutes is proposed for Malarone Tablets and Q = [redacted] at 45 minutes for Malarone Pediatric Tablets.

Table C1. Atovaquone Dissolution Data for Typical Production Batches of MALARONE® Tablets

Batch	Time	Percent Atovaquone Dissolved (based on label claim)		
		Individual Tablets	Avg.	%RSD
7D538	15 min			
Age: 32 months	30 min			
	45 min			
	60 min			
1E415	10 min			
Age: 3 months	20 min			
	30 min			
	45 min			
	60 min			
1E416	10 min			
Age: 3 months	20 min			
	30 min			
	45 min			
	60 min			

Figure C1. Atovaquone Dissolution Profile for Typical Production Batches of MALARONE® Tablets

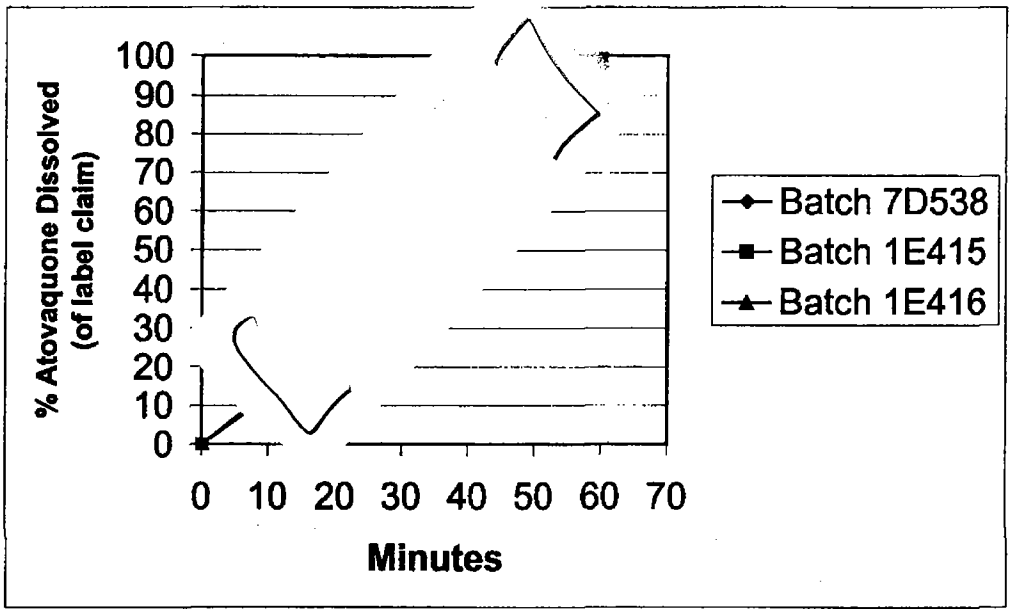
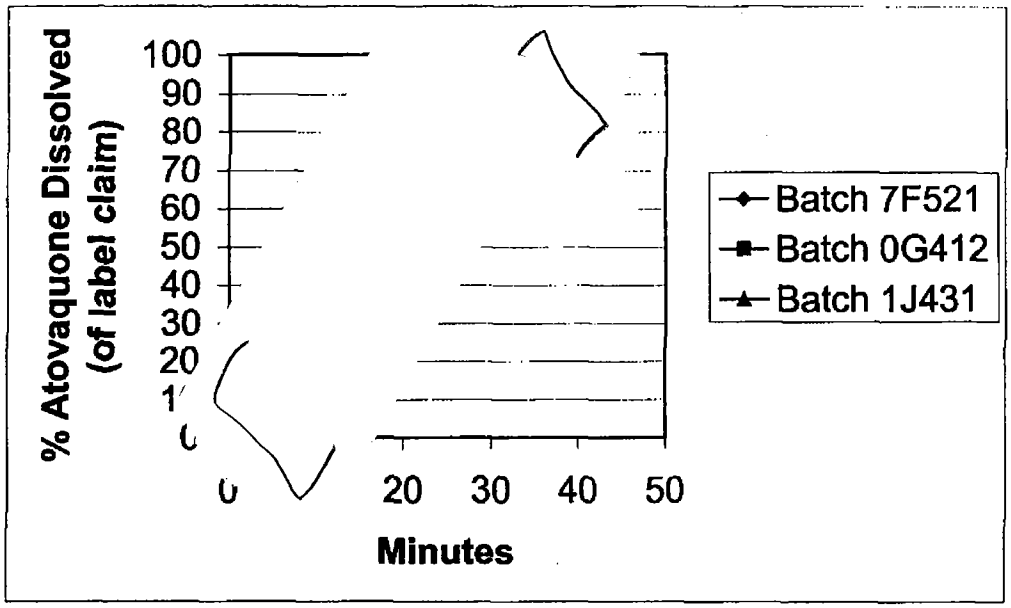


Table C2. Atovaquone Dissolution Data for Typical Production Batches of MALARONE® Pediatric Tablets

Batch	Time	Percent Atovaquone Dissolved (based on label claim)		
		Individual Tablets	Avg.	%RSD
7F521	15 mi			
Age: 48 months	30 n			
	45 mi			
0G412	10 mi			
Age: 15 months	20 min			
	30 min			
	45 min			
1J431	10 r			
Age: 1 month	20 min			
	30 min			
	45 min			

Figure C2. Atovaquone Dissolution Profile for Typical Production Batches of MALARONE® Pediatric Tablets



Assay Method and Validation

Parameter	Results	
	Malarone Tabl	Malarone Ped
Limit of Quantification		
Linearity		
Specificity		
Inter-assay precision		
Intra-assay precision		
Inter-assay accuracy		
Intra-assay accuracy		
Standard Solution Stability		
Recovery		

Conclusions

The sponsor used [redacted] to help avoid coning of tablets during dissolution. In addition, the sponsor used a [redacted] in the dissolution medium because the [redacted]. Both of these implementations to the dissolution method are seen as an unconventional. The sponsor have tried to develop a dissolution method that avoids using extreme conditions or one that is more reflective of physiological conditions but have been unsuccessful up to this point. The reviewer of the Mepron (atovaquone) tablet application, NDA 20-259, requested an evaluation from the Division of Biopharmaceutics Research Laboratory for an alternate dissolution method and the Division of Biopharmaceutics Research Laboratory responded to his request by assessing several dissolution methods for atovaquone. They are the following:

Method: USP Paddle
Speed: 50 rpm
Media:

- 1000 mL of SIF, pH 7.5 phosphate buffer with 0.5% of the surfactant cetyl trimethyl ammonium bromide (CTAB)
- SIF + 0.2% CTAB
- SIF + 0.5% CTAB
- pH 6.8 phosphate buffer + 0.5% CTAB

The sponsor tried the following media to replicate the results obtained by the Division of Biopharmaceutics Research Laboratory and was not able to reproduce the results. These media are:

- 1000 mL SIF without enzymes + 0.5% CTAB
- 900 mL of USP pH 6.8 buffer + 0.5% CTAB
- 1000 mL SIF without enzymes + 2.0% CTAB
- 900 mL of USP pH 6.8 buffer + 2.0% CTAB

The results from these media were submitted to IND 50,247 (Malarone Tablets and Pediatric Tablets) in correspondence dated October 16, 1998.

Also, during the development of the dissolution method, the sponsor investigated isopropyl alcohol (IPA) at different concentrations (0-50%) in borate buffer (pH 10). The results indicated that a minimum of approximately 40% v/v IPA is required to achieve complete dissolution of atovaquone.

It was noted that in the two batches of Malarone tablets submitted under this cover, batches no. 7D538 and 1E415, two individual vessels had failed results (below Q+5%) as seen in Table C1, cell 6 at 45 minutes for batch 7D538 and cell 3 at 45 minutes for batch 1E415. In addition, the profile of Malarone Pediatric Tablet batches are less discriminatory and dissolve faster as they age. The sponsor did not provide an explanation to this phenomenon.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information contained in this submission and has found it to be acceptable. There are three comments to be conveyed to the sponsor and are provided below.

General Comments (not to be sent to sponsor)

Although the use of the [redacted] e not conventional, it is justifiable for this drug substance.

Comments (to be sent to sponsor)

- Please provide an explanation of why malarone pediatric tablets dissolve faster with age.
- Please provide dissolution data at release of the commercial batches manufactured recently of malarone tablets and malarone pediatric tablets.

Houda Mahayni, R.Ph., Ph.D.

Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

FT/RD initialed by Barbara Davit, Ph.D., Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Houda Mahayni
5/10/02 04:50:04 PM
BIOPHARMACEUTICS

Barbara Davit
5/10/02 05:07:35 PM
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