CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-188

ADMINISTRATIVE DOCUMENTS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #75-188 **SPONSOR:** Alphapharm PTY. LTD.
Drug: Amiodarone HCl
DOSAGE FORM: Tablets
STRENGTH: 200 mg
TYPE OF STUDY: Single-dose, Fasting Study
CLINICAL SITE:
ANALYTICAL SITE:

STUDY SUMMARY:

The single-dose bioequivalence study conducted under fasting conditions was found acceptable by the Division of Bioequivalence.

DISSOLUTION:

The dissolution testing was found acceptable.

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE: /S/ F Nouravarsani **DATE:** 9/11/1998

Acting Team Leader: B. Davit **BRANCH:** III

SIGNITURE: /S/ **DATE:** 9/12/98

DIRECTOR: Dale P. Conner
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: /S/ **DATE:** 9/19/98

DIRECTOR: Doug Sporn
OFFICE OF GENERIC DRUGS:

SIGNITURE: _____ **DATE:** _____

DIVISION REVIEW SUMMARY

ANDA: 75-188

FIRM:

Par Pharmaceuthical, Inc.
U. S. Agent for: Alphapharm Pty. Ltd.

DOSAGE FORM: Tablets STRENGTH: 250 mg

DRUG: Amiodarone hydrochloride

CGMP STATEMENT/EIR UPDATE STATUS

GMP certification statement is presented (p. 2741).

Firm and drug substance manufacturer found in compliance, February 24, 1998 and Micron Technologies on February 23, 1998.

BIO STUDY INFORMATION:

On October 23, 1998 the firm was advised that the Division of Bioequivalence has completed its review and has no further questions at this time. The firm was directed to incorporate into their stability and quality control programs the following dissolution testing:

The testing should be conducted in 900 mL of pH 5 Disodium Acetate Buffer with 1.0% (w/v) Sodium Lauryl Sulphate at 37° C using USP 23 Apparatus 2 (paddle) at 75 rpm.

The test should meet the following specifications:

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)

Validation of the upgraded analytical methods are included as follows:

The related substance assay method was found to have selectivity and sensitivity for the semi-quantitation of 2-butyl-3-(4-hydroxy-3,5-diiodobenzoyl)benzofuran, mono iodo amiodarone, bis desiodo amiodarone and (2-chloroethyl)diethylamine hydrochloride (pp. 3286 -

The limits of detection are of the limits concentration for 2-butyl-3-(4-hydroxy-3,5-diiodobenzoyl)benzofuran and (2-chloroethyl)diethylamine hydrochloride, of the limit concentration for mono iodo amiodarone and bis desiodo amiodarone, and . of the ½ limit concentration for multiple unknown impurities. The method was found to be stability indicating (pp. 3286 - 3299). It is noted that the "photographs" of the plates presented range from poor to illegible copies (pp. 3288 -3299)

The esidual solvents were found to have selectivity and sensitivity for the quantitation of ethanol, acetone, and dichloromethane in the presence of 100% drug substance.

It is noted that chloroform gave results linear and precise, but had a poor recovery: . The firm recommended that the limit for chloroform be reduced from NMT to NMT to allow for the poor recovery (pp. 3300 -3306).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

Yes, as per the following configuration:

Batch No.	Container/closure	Storage	Time stations
PM009	1000's in 500 mL bottle	30°C (pp. 89 - 90) 40°C/75% RH (p. 91)	6, 9 & 12 months 6 months

PM009A	60's in 40 mL ____ bottle	30°C (pp. 92 - 93) 40°C/75% RH (p. 94)	6, 9 & 12 months 6 months
PM009B	Blisters (250 µm, 40g/m²)	30°C (pp. 95 -96) 40°C/75% RH (p. 97)	6, 9 & 12 months 6 months
PM009C	Bulk, 20 L container	20°C (p. 99)	6 months
PM009C*	Bulk, 4 L container	25°C/60 RH (p. 98)	6 months

2. Please find appended the revised Stability Specifications.

LABELING:

A telephone amendment was submitted to the firm on October 23, 1998. Satisfactory. See review dated 11/24/98.

STERILIZATION VALIDATION (IF APPLICABLE)

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

units, executed batch record, lot No. PM009.

Amiodarone Hydrochloride, DMF found adequate on 12/19/97

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Same size, tablets and batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

units, same process.

RECOMMENDATION:

Approvable.

SIGNATURE: 1/21/99

DATE: January 14, 1999

A. Croitoru

COMPONENTS AND COMPOSITION

The following qualitative and quantitative statements are presented:

AMIODARONE Components	mg/tablet
[illegible]	[illegible]

Amiondarone Hydrochloride, drug substance, test, specifications and test results:

Test	Specification	Result
Characteristics		Complies
Identification		
		Complies
		Not tested
		Complies
Appearance of solution		Complies
pH		3.22

Related substances		%	
Iodides			
Heavy metals			
Loss on drying			
Sulfated ash			
Assay			
Particle size			
Residual Solvents			

Drug product test, specification and test results for the executed batch No. PM009:

Test	Specification	Result
Appearance		
Uniformity of tablet weight (BP93 p. 753)		
Identification (BP93 Add. 95 p. 1629)		
Related substances (in-house)		
Uniformity of dosage units (USP XXIII p. 1838)		
Assay (BP93 Add. 95 p. 1629)		

Dissolution
(in-house)

cc: ANDA 75-188

Endorsements:
HFD-645/ACroitoru/1/14/99
HFD-645/BTArnwine/1/19/99

R. & D. STABILITY SPECIFICATION

AMIODARONE HYDROCHLORIDE TABLETS 200 mg

(contains 200 mg Amiodarone Hydrochloride)

AMIUS200.RS

Doc.No.: RDLSS-04-365/200-3(US)	Supercedes: RDLSS-04-365/200-2(US)	Rev: 01/2004
R.M. No: 365	Pharmacopoeial Reference: BP 1993 Addendum 95	
Prepared by: [illegible] Date: 07.01.99	Checked by: [illegible] Date: 7/1/99	Approved by: [illegible] Date: 7/1/99

Specification for: USA

TEST	SPECIFICATION
1. APPEARANCE:	
2. IDENTIFICATION: (BP93 Add 95 p1629)	...chromatogram obtained with the Sample Preparation.
3. DISSOLUTION: (OGD,CDER Mar 97)	
4. RELATED SUBSTANCES: (BP93 Add 95 p1629; In-house mod.)	
5. AVERAGE TABLET WEIGHT:	
6. ASSAY: (In-house)	

R. & D. STABILITY

RECORD OF MASTER DOCUMENT UPDATES (CONTINUED)

PRODUCT: Amiodarone HCl Tablets 200 mg **MASTER DOCUMENT NO.**: RDLS-04-365/200(US)

AMIUS200.RFU

DATE	DOCUMENT NO./S	REASON FOR UPDATE
1/97	RDLST-04-365/200-1(US) RDLSA-04-365/200-1(US)	1. 2. 3.
3/97	RDLSS-04-365/200-1(US) RDLST-04-365/200-2(US)	1. 2.
6/97	RDLSA-04-365/200-2(US)	1.
7/97	RDLSS-04-365/200-2(US)	1. 2.
7/97	RDLST-04-365/200-3(US)	1.
10/97	RDLST-04-365/200-4(US)	1.
1/99	RDLSS-04-365/200-3(US)	1.