

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-807**

**CHEMISTRY REVIEW(S)**



## **NDA 50-807**

**Epirubicin Hydrochloride  
for Injection,  
50 mg/vial, 200 mg/vial**

**Mayne Pharma (USA) Inc.**

**Xiao-Hong Chen, Ph.D.  
Division of Pre-Marketing Assessment III &  
Manufacturing Science  
Branch V**



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# Chemistry Review Data Sheet

1. NDA 50-807
2. REVIEW #1:
3. REVIEW DATE: March 23, 2006
4. REVIEWER: Xiao-Hong Chen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA submission  
 Amendment  
 Amendment  
 Amendment  
 Amendment  
 Amendment  
 Amendment

July 15, 2005  
 April 21, 2006  
 April 28, 2006  
 June 16, 2006  
 June 21, 2006  
 July 14, 2006  
 July 14, 2006

7. NAME & ADDRESS OF APPLICANT:

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Name: Mayne Pharma (USA) Inc.  
Address: One Franklin Plaza  
P.O. Box 7929  
Philadelphia, PA 19101  
Representative: Ellen Cutler  
Telephone: (215) 751-4000

8. DRUG PRODUCT EPIRUBICIN HYDROCHLORIDE/CODE/TYPE:

- a) Proprietary Name: Epirubicin Hydrochloride for Injection®
- b) Non-Proprietary Name (USAN): Epirubicin Hydrochloride
- c) Code Name/#: N/A
- d) Chem. Type/Submission Priority (ONDPA only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Filed 505(b)(2)

10. PHARMACOL. CATEGORY: a component of adjuvant therapy in patients with evidence of auxiliary node tumor involvement following resection of primary breast cancer

11. DOSAGE FORM: Injection, Powder, Lyophilized, for Solution, (705)

12. STRENGTH/POTENCY: 50 mg/vial, 200 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous (002)

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

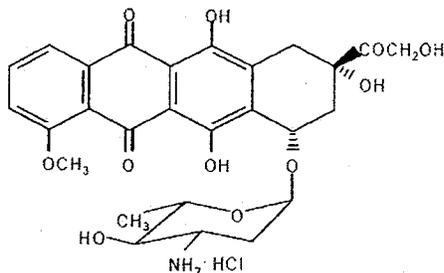
\_\_\_\_\_ SPOTS product – Form Completed

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X  Not a SPOTS product

16. CHEMICAL EPIRUBICIN HYDROCHLORIDE, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name Epirubicin Hydrochloride  
 Chemical Name (8S-cis)-10-[(3-amino-2,3,6-trideoxy-α-L-arabinopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-rihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride  
 CAS number 56390-09-1  
 Molecular Weight 580  
 Molecular Formula C<sub>27</sub>H<sub>29</sub>NO<sub>11</sub>·HCl  
 Structural formula See above

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
I	II		Epirubicin hydrochloride	1	Adequate	10-26-2006	Dr. Xiao Hong Chen
	III			3	Adequate	10-26-2000	Dr. A. Raw
	III			3	Adequate	10-22-2002	Dr. Allan Fenselau
	II			1	Adequate	6-27-2006	Dr. Xiao Hong Chen

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<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

IND 69,448	Pre-IND Meeting	May 19, 2004.
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**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	19-Sep-2005	Office of Compliance
ODS/DMETS	Revisions to the labels	12-APR- 2006	Nora Roselle, PharmD
Methods Validation	May be submitted post approval		Xiao Hong Chen
EA (Categorical exclusion)	N/A	23-Mar-2006	Xiao Hong Chen
Microbiology	Acceptable	26-JUN- 2006	John Metcalfe
Pharm/Tox	Not consulted		Xiao Hong Chen
Biopharm	Not consulted		Xiao Hong Chen

# The Chemistry Review for NDA 50-807

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for approval. The applicant has satisfactorily addressed all CMC deficiencies. The DMF — as amended on June 8, 2006, has been reviewed and found to be adequate. The Office of Compliance has provided an overall "acceptable" recommendation for this application.

We recommend that the following comment regarding shelf life be included in the approval letter:

An expiration-dating period of 18 months for the drug product is granted based on stability data provided.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable.

N/A.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Product

Epirubicin Hydrochloride for Injection is an anthracycline cytotoxic agent, intended for intravenous administration. Epirubicin Hydrochloride for Injection is supplied as a sterile, orange-red, lyophilized powder in single-dose vials containing 50 mg or 200 mg of epirubicin. Each 50 mg and 200 mg vial contains 250 mg and 1000 mg lactose, respectively.

This 505(b)(2) application references clinical studies demonstrating safety and efficacy for the Reference Listed Drug, Ellence® (epirubicin hydrochloride injection), marketed by Pfizer, submitted in NDA 50-778, approved September 15, 1999. Epirubicin Hydrochloride for Injection contains the same active ingredient and strengths as the Pfizer's RLD, Ellence. Ellence is a solution dosage form, and Epirubicin HCl for Injection was developed as a lyophilized powder for reconstitution intended to have a longer shelf life. Upon reconstitution, the Mayne product is the same as the Pfizer product, i.e. an injectable

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solution with an epirubicin hydrochloride concentration of 2 mg/mL. Lactose monohydrate, NF is used \_\_\_\_\_ The RLD is pH adjusted with HCl to pH 3 since it is known that Epirubicin HCl is stable at a pH below 5. The proposed Mayne's product is freeze-dried, and therefore would be expected to have improved stability when compared to a solution product, thus eliminating the need for pH adjustment.

Epirubicin HCl for Injection is manufactured in Mayne Pharma's plant in Mulgrave, Australia, where a number of similar dosage forms are also manufactured. Drug product manufacturing process involves \_\_\_\_\_

\_\_\_\_\_ The drug product is packaged into 30 mL and 100 mL clear \_\_\_\_\_ glass vials, and stoppered with \_\_\_\_\_ closure.

**Drug Substance**

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The NDA is recommended for approval from the CMC perspective as the applicant has adequately addressed all deficiencies and there are no outstanding issues. DMF — has been found to be adequate, and the Office of Compliance has provided an “acceptable” recommendation for the cGMP requirements.

**III. Administrative**

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: Xiao Hong Chen, Ph.D.  
Branch Chief Name/Date: Ravi Harapanhalli, Ph.D.  
Project Manager Name/Date: Paul Zimmerman

C. CC Block

**APPEARS THIS WAY  
ON ORIGINAL**

94 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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/s/

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Xiao Hong Chen  
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Ravi Harapanhalli  
7/25/2006 06:08:12 PM  
CHEMIST

ONDQA Memo to NDA File for  
NDA 50-807 Epirubicin Hydrochloride for Injection  
50 mg/vial, 200 mg/vial  
Date: August 11, 2006

DMETS has expressed concern that the so-called tall-man lettering of epirubicin as EPIrubicin within the name may create confusion and potentially lead to medication errors whereby this drug product containing the word, EPIrubicin may be accidentally substituted for drug products containing the word EPInephrine. Some EPInephrine drug products also use the tall-man lettering for the same first three letters (EPI) to distinguish it from Ephedrine containing drug products. Also, epinephrine is well known by the common colloquial name of "epi".

There is also a concern that Epirubicin may be confused with other cytotoxic agents containing "rubicin" in their name. For example, DOXOrubicin uses the tall-man letters "DOXO" to distinguish it from Daunorubicin on drug product labeling.

It is difficult to predict the likelihood of these two medication errors; that is:

1. EPIrubicin for EPInephrine versus
2. Epirubicin for Daunorubicin or DOXOrubicin.

It is clear that error #2 above is highly undesirable. However, it also seems clear that error #1 above would almost certainly be fatal in situations where epinephrine is often used (anaphylaxis, other severe allergic reactions, cardiac arrest).

Based on the overall weight of the consequence of medication error #1, CMC concurs with DMETS and the DODP to ask the applicant to remove the tall-man lettering from the word EPIrubicin and change it to Epirubicin in all of their labeling.

Respectfully submitted

Richard (Rik) Lostritto, Ph.D., Director  
ONDQA, Division-III

Rik Lostritto, Ph.D., Director  
ONDQA, Division-III

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/s/  
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Richard Lostritto  
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