

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-718/S-46

Trade Name: Doxil®

Generic Name: doxorubicin hydrochloride liposome injection

Sponsor: Janssen Products, L.P.

Approval Date: January 22, 2015

Indications: For the treatment of ovarian cancer, AIDS-related Kaposi's Sarcoma and multiple myeloma.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 50-718/S-46

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

APPROVAL LETTER



NDA 50718/S-046

SUPPLEMENT APPROVAL

Janssen Products, L.P.
Attention: Matthew Scurato
Associate Director, Global Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Scurato:

Please refer to your Supplemental New Drug Application (sNDA) dated July 12, 2013, received July 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doxil (doxorubicin HCl liposome injection), 20 mg/10 mL and 50 mg/25 mL.

We acknowledge receipt of your amendments to this supplement dated August 16, 2013, August 28, 2013, September 22, 2014, October 1, 2014, January 9, 2015, January 16, 2015, January 20, 2015, and January 22, 2015.

The September 22, 2014, submission constituted a complete response to our November 12, 2013, Complete Response action letter.

This Prior Approval supplemental new drug application provides for:

- a new manufacturing site, TTY Biopharm Company Limited (TTY Biopharm) located in Chungli, Taoyuan, Taiwan, R.O.C. for the manufacturing of the drug product;
- a change in batch size of the drug product to (b) (4) and drug product manufacturing process changes;
- a new (b) (4) stopper for the drug product container/closure system;
- addition of a secondary packaging site at (b) (4) .;
- revisions of the package insert to conform with the requirements of content and format of labeling as described in 21 CFR 201.56 and 201.57, and the Pregnancy and Lactation Labeling Rule (PLLR); and,
- revisions of carton and immediate container labeling to mitigate the risk of medication errors.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.”

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to carton and immediate-container labels submitted on January 9, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 50718/S-046.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Anuja Patel, Senior Regulatory Health Project Manager, at (301) 796-9022.

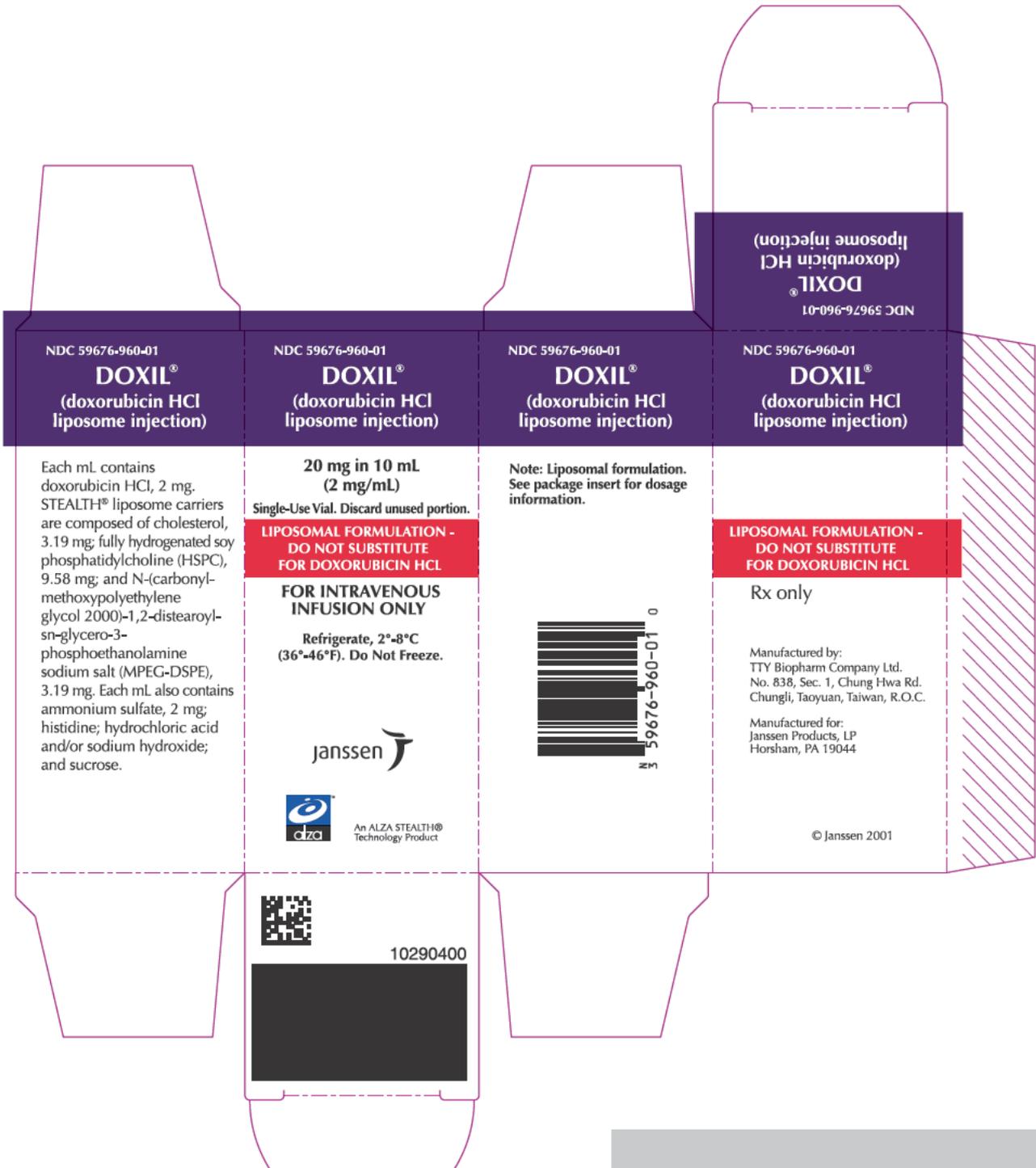
Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Package Insert Labeling
Carton and Container Labeling



NDC 59676-960-01

DOXIL[®]
(doxorubicin HCl liposome injection)

Each mL contains doxorubicin HCl, 2 mg. STEALTH[®] liposome carriers are composed of cholesterol, 3.19 mg; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg; and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg. Each mL also contains ammonium sulfate, 2 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.

NDC 59676-960-01

DOXIL[®]
(doxorubicin HCl liposome injection)

**20 mg in 10 mL
(2 mg/mL)**

Single-Use Vial. Discard unused portion.

**LIPOSOMAL FORMULATION -
DO NOT SUBSTITUTE
FOR DOXORUBICIN HCL**

**FOR INTRAVENOUS
INFUSION ONLY**

Refrigerate, 2°-8°C
(36°-46°F). Do Not Freeze.

janssen



An ALZA STEALTH[®]
Technology Product

NDC 59676-960-01

DOXIL[®]
(doxorubicin HCl liposome injection)

Note: Liposomal formulation.
See package insert for dosage
information.



NDC 59676-960-01

DOXIL[®]
(doxorubicin HCl liposome injection)

**LIPOSOMAL FORMULATION -
DO NOT SUBSTITUTE
FOR DOXORUBICIN HCL**

Rx only

Manufactured by:
TTY Biopharm Company Ltd.
No. 838, Sec. 1, Chung Hwa Rd.
Chungli, Taoyuan, Taiwan, R.O.C.

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

© Janssen 2001



10290400

(b) (4)

(b) (4)

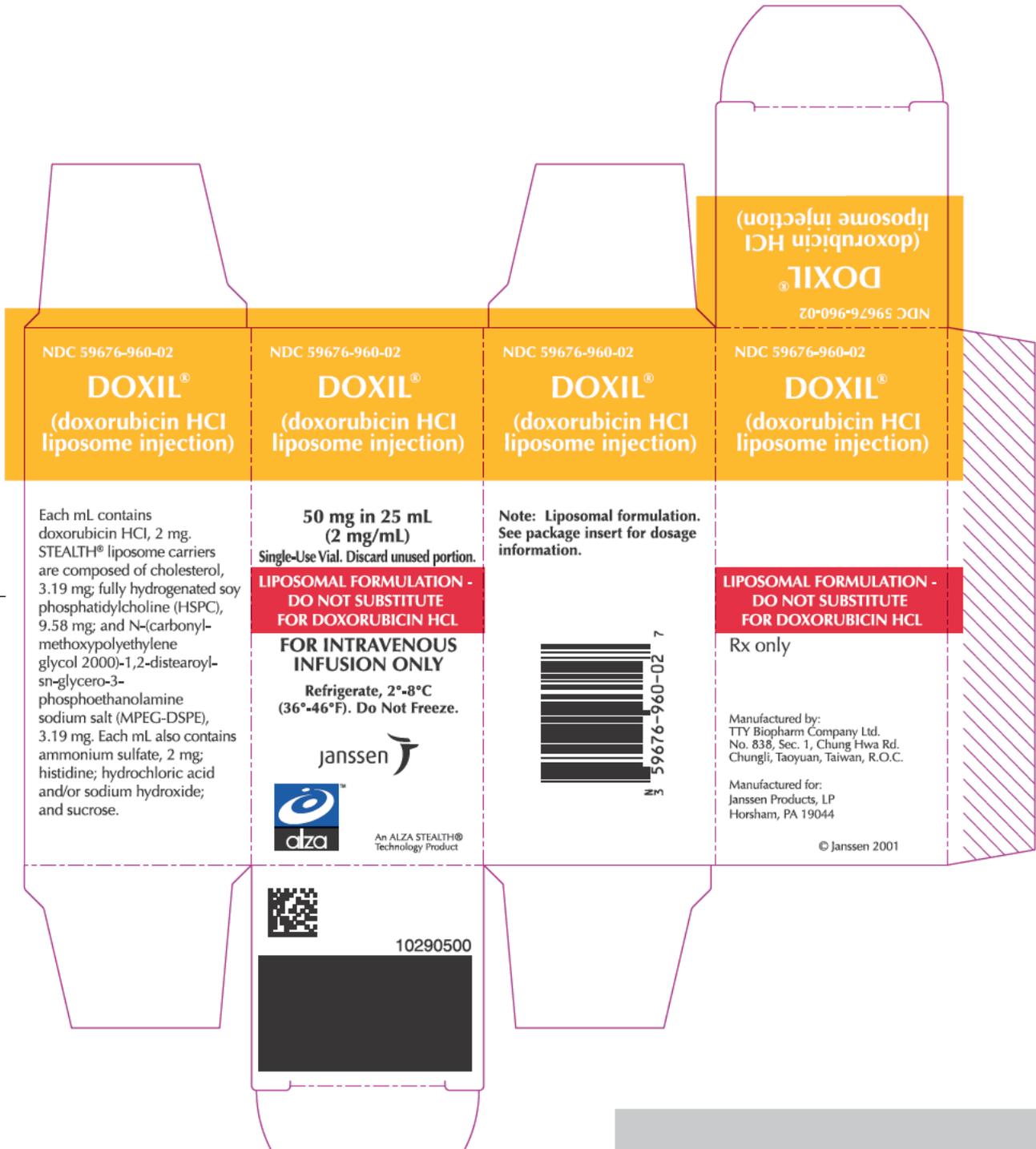
Note: Keyline does not print.



(b) (4)



(b) (4)



NDC 59676-960-02

DOXIL[®]
(doxorubicin HCl liposome injection)

Each mL contains doxorubicin HCl, 2 mg. STEALTH[®] liposome carriers are composed of cholesterol, 3.19 mg; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg; and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg. Each mL also contains ammonium sulfate, 2 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.

NDC 59676-960-02

DOXIL[®]
(doxorubicin HCl liposome injection)

50 mg in 25 mL (2 mg/mL)
Single-Use Vial. Discard unused portion.

LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL

FOR INTRAVENOUS INFUSION ONLY
Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.

janssen



An ALZA STEALTH[®] Technology Product

NDC 59676-960-02

DOXIL[®]
(doxorubicin HCl liposome injection)

Note: Liposomal formulation. See package insert for dosage information.



NDC 59676-960-02

DOXIL[®]
(doxorubicin HCl liposome injection)

LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL

Rx only

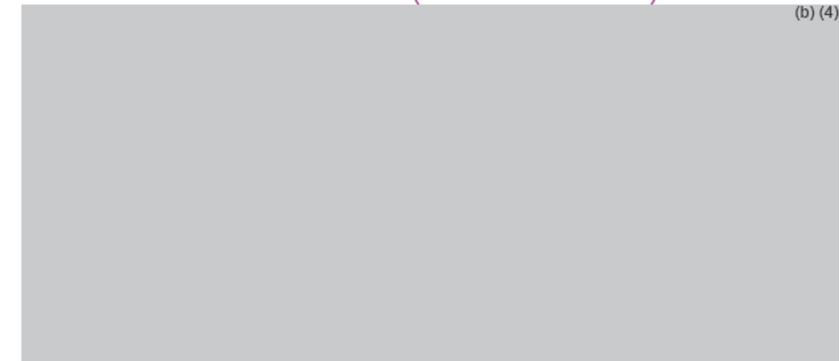
Manufactured by:
TTY Biopharm Company Ltd.
No. 838, Sec. 1, Chung Hwa Rd.
Chungli, Taoyuan, Taiwan, R.O.C.

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

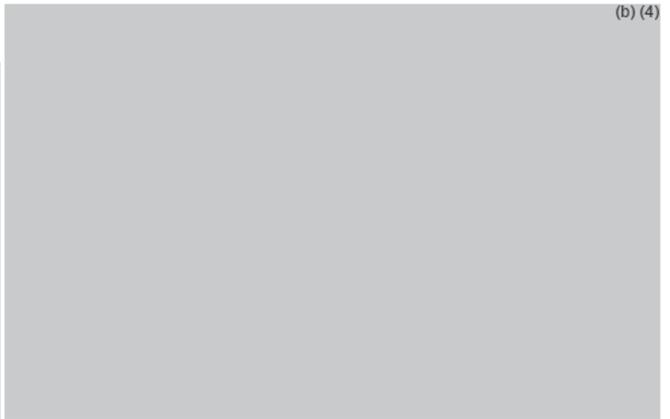
© Janssen 2001



10290500



(b) (4)



(b) (4)

Note: Keyline does not print.

NDC 59676-960-02

DOXIL[®]
(doxorubicin HCl liposome injection)

50 mg in 25 mL
(2 mg/mL)

Single-Use Vial. Discard unused portion.

LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL

FOR INTRAVENOUS INFUSION ONLY
Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.
See package insert for dosage information.
Rx ONLY

0100359676960027

Janssen

© Janssen 2001

10290300

Manufactured by:
TTY Biopharm Company Ltd.
No. 838, Sec. 1, Chung Hwa Rd.
Chungli, Taoyuan, Taiwan, R.O.C.

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

 **CRYO**
AN ALZ STEARIS[®] TECHNOLOGY PRODUCT



(b) (4)

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

/s/

PATRICIA KEEGAN
01/22/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

OTHER ACTION LETTER(S)



NDA 50718/S-046

COMPLETE RESPONSE

Janssen Products, L.P.
Attention: Naushad Islam, M.S., R.Ph.
Director, Global Regulatory Affairs
Janssen Research & Development LLC
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Dear Mr. Naushad:

Please refer to your Supplemental New Drug Application (sNDA) dated July 12, 2013, received July 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doxil (doxorubicin HCl liposome injection), 20 mg/10 mL and 50 mg/25 mL.

We acknowledge receipt of your amendments to this supplement, dated August 16, 2013, and August 28, 2013.

This Prior Approval Supplemental New Drug Application provides for:

- a new manufacturing site, TTY Biopharm Company Limited (TTY Biopharm) located in Chungli, Taoyuan, Taiwan, R.O.C. for the manufacturing process and (b) (4) operations of the drug product;
- a change in batch size of the drug product to (b) (4);
- a new (b) (4) stopper for the drug product;
- addition of a secondary packaging site at (b) (4) and,
- a request for waiver from the requirement to support the proposed manufacturing changes by conducting a bioequivalence (BE) study; the waiver is supported by the results of a nonclinical bioequivalence assessment.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action and, where possible, our recommendations to address the issues.

PRODUCT QUALITY and BIOPHARMACEUTICS

1. On multiple occasions, FDA has provided advice to Janssen on the need for BE study to support certain manufacturing changes (e.g. new manufacturing site). Specifically, we refer to the meetings, teleconferences, and letters/memos held or issued on the following dates which contained not only our advice but the rationale for why such studies would be required:

Under NDA 50718

- January 13, 2012, Type A Meeting (Minutes issued February 9, 2012)
- March 2, 2012, Letter regarding your February 10, 2012 Protocol Element Document for the Bioequivalence Study
- August 21, 2012, Type C Teleconference (Minutes issued September 18, 2012)
- February 26, 2013, Teleconference
- July 25, 2013, Teleconference

Under IND 36,778

- April 25, 2013, e-mail communication from Ms. Anuja Patel regarding the March 20, 2013, submission containing Protocol DOXILNAP1002 (bioequivalence protocol)
- May 24, 2013, e-mail communication from Ms. Anuja Patel requesting CMC information to support the March 20, 2013, submission containing Protocol DOXILNAP1002 (bioequivalence protocol)

For the reasons previously conveyed to you in the communications above, we will not grant your request for waiver from the requirements to conduct a BE study. The animal BE data provided in this supplement cannot substitute for human BE data in support of a change in a manufacturing site for your doxorubicin HCl liposome injection drug product, which is a modified release dosage form.

To qualify the new manufacturing site at TTY, Taiwan, a BE study is required. You must conduct and submit the results of the BE study, DOXILNAP1002 entitled, "A Pivotal Bioequivalence Study of DOXIL/CAELYX Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies including Subjects with Ovarian Cancer."

Alternatively, you may address this deficiency by providing additional data to support a request for a waiver from the requirement to conduct a BE study. Such data may include demonstration of robust results in an In-vitro In-vivo Correlation (IVIVC) model for Doxil in which IVIVC is confirmed. Because you previously failed to establish IVIVC, your assessment of the robustness of the new IVIVC model must include a consideration of the previous results.

2. In section "3.2.P.2.3 Manufacturing Process Development," the in vitro drug leakage and in vitro drug release assay under multiple pH conditions were assessed. However, the sample sizes, the variability in each test, the data for each individual unit and the similarity factor f_2 values were not provided. In your response, submit the following information:
 - a. The sample sizes and individual data with the variability (standard deviation and/or CV) for each lot used in each of the drug leakage and the in vitro drug release tests.

- b. The similarity factor f2 values for the profile comparisons using (b) (4) units of each lot per test.
3. Provide data, or your justification for not providing data, regarding the potential leachables/extractables that could impact the drug product from the use of the proposed new (b) (4) stoppers.

LABELING COMMENTS

4. Submit draft labeling that incorporates the preliminary revisions identified in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

5. Please submit draft carton and container labeling revised as per the following preliminary comments:
 - a. Revise the total drug content and strength per milliliter statement to appear in a stacked format, similar to:

20 mg in 10 mL
(2 mg/mL)
 - b. Change statement, (b) (4) to read “Single (b) (4) Vial. Discard unused portion.”

6. The Doxil 20 mg and 50 mg container labels and carton labeling present the claim, (b) (4)


7. Please change the statement (b) (4) to “Do Not Freeze.”
8. Please delete the statement (b) (4)

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Anuja Patel, Regulatory Health Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

37 page(s) has been Withheld In Full as b4 (CCI/TS) immediately following this page

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

/s/

PATRICIA KEEGAN
11/12/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOXIL safely and effectively. See full prescribing information for DOXIL.

DOXIL® (doxorubicin hydrochloride liposome injection), for intravenous use

Initial U.S. Approval: 1995

WARNING: CARDIOMYOPATHY and INFUSION-RELATED REACTIONS

See full prescribing information for complete boxed warning.

- Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². The risk of cardiomyopathy may be increased at lower cumulative doses with mediastinal irradiation (5.1).
- Acute infusion-related reactions occurred in 11% of patients with solid tumors. Serious, life-threatening, and fatal infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).

RECENT MAJOR CHANGES

Boxed Warning	01/2015
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7)	01/2015
Contraindications (4)	01/2015
Warnings and Precautions (5.1, 5.2, 5.3, 5.5)	01/2015

INDICATIONS AND USAGE

DOXIL is an anthracycline topoisomerase II inhibitor indicated for:

- **Ovarian cancer (1.1)**

After failure of platinum-based chemotherapy.

- **AIDS-related Kaposi's Sarcoma (1.2)**

After failure of prior systemic chemotherapy or intolerance to such therapy.

- **Multiple Myeloma (1.3)**

In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING—CARDIOMYOPATHY, INFUSION-RELATED REACTIONS

1 INDICATIONS AND USAGE

- 1.1 Ovarian Cancer
- 1.2 AIDS-Related Kaposi's Sarcoma
- 1.3 Multiple Myeloma

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Use Information
- 2.2 Ovarian Cancer
- 2.3 AIDS-Related Kaposi's Sarcoma
- 2.4 Multiple Myeloma
- 2.5 Dose Modifications for Adverse Reactions
- 2.6 Preparation and Administration
- 2.7 Procedure for Proper Handling and Disposal

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Cardiomyopathy
- 5.2 Infusion-Related Reactions
- 5.3 Hand-Foot Syndrome (HFS)
- 5.4 Secondary Oral Neoplasms
- 5.5 Embryofetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Adverse Reactions in Clinical Trials
- 6.2 Postmarketing Experience

DOSAGE AND ADMINISTRATION

Administer DOXIL at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, increase rate of infusion to complete administration over 1 hour. Do not administer as bolus injection or undiluted solution (2).

- **Ovarian cancer:** 50 mg/m² IV every 4 weeks (2.2)
- **AIDS-related Kaposi's Sarcoma:** 20 mg/m² IV every 3 weeks (2.3)
- **Multiple Myeloma:** 30 mg/m² IV on day 4 following bortezomib (2.4)

DOSAGE FORMS AND STRENGTHS

Doxorubicin hydrochloride (HCl) liposomal injection: Single use vials: 20 mg/10 mL and 50 mg/25 mL (3)

CONTRAINDICATIONS

- Hypersensitivity reactions to doxorubicin HCl or the components of DOXIL (4, 5.2)

WARNINGS AND PRECAUTIONS

- Hand-Foot Syndrome may occur. Dose modification or discontinuation may be required (5.3)
- Embryofetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus. Use effective contraception (5.5, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (>20%) are asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand-foot syndrome, rash, neutropenia, thrombocytopenia, and anemia (6).

To report SUSPECTED ADVERSE REACTIONS contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue breastfeeding (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised:
01/2015

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NON-CLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Ovarian Cancer
- 14.2 AIDS-Related Kaposi's Sarcoma
- 14.3 Multiple Myeloma

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY and INFUSION-RELATED REACTIONS

- **DOXIL (doxorubicin HCl liposome injection) can cause myocardial damage, including congestive heart failure, as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². In a clinical study of 250 patients with advanced cancer who were treated with DOXIL, the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was between 450-550 mg/m². Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. The risk of cardiomyopathy may be increased at lower cumulative doses in patients with prior mediastinal irradiation [see Warnings and Precautions (5.1)].**
- **Acute infusion-related reactions consisting of, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension occurred in 11% of patients with solid tumors treated with DOXIL. Serious, life-threatening and fatal infusion reactions have been reported [see Dosage and Administration (2.6) and Warnings and Precautions (5.2)].**

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

DOXIL is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

1.2 AIDS-Related Kaposi's Sarcoma

DOXIL is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.

1.3 Multiple Myeloma

DOXIL, in combination with bortezomib, is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

Do not substitute DOXIL for doxorubicin HCl injection.

Do not administer as an undiluted suspension or as an intravenous bolus [see Warnings and Precautions (5.2)].

2.2 Ovarian Cancer

The recommended dose of DOXIL is 50 mg/m² intravenously over 60 minutes every 28 days until disease progression or unacceptable toxicity.

2.3 AIDS-Related Kaposi's Sarcoma

The recommended dose of DOXIL is 20 mg/m² intravenously over 60 minutes every 21 days until disease progression or unacceptable toxicity.

2.4 Multiple Myeloma

The recommended dose of DOXIL is 30 mg/m² intravenously over 60 minutes on day 4 of each 21-day cycle for eight cycles or until disease progression or unacceptable toxicity.

Administer DOXIL after bortezomib on day 4 of each cycle [*see Clinical Studies (14.3)*].

2.5 Dose Modifications for Adverse Reactions

Do not increase DOXIL after a dose reduction for toxicity.

Table 1: Recommended Dose Modifications for Hand-Foot Syndrome, Stomatitis, or Hematologic Adverse Reactions

Toxicity	Dose Adjustment
Hand-Foot Syndrome (HFS)	
Grade 1: Mild erythema, swelling, or desquamation not interfering with daily activities	<ul style="list-style-type: none"> If no previous Grade 3 or 4 HFS: no dose adjustment. If previous Grade 3 or 4 HFS: delay dose up to 2 weeks, then decrease dose by 25%.
Grade 2: Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	<ul style="list-style-type: none"> Delay dosing up to 2 weeks or until resolved to Grade 0-1. Discontinue DOXIL if no resolution after 2 weeks. If resolved to Grade 0-1 within 2 weeks: <ul style="list-style-type: none"> <u>And</u> no previous Grade 3 or 4 HFS: continue treatment at previous dose. <u>And</u> previous Grade 3 or 4 toxicity: decrease dose by 25%.
Grade 3: Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	<ul style="list-style-type: none"> Delay dosing up to 2 weeks or until resolved to Grade 0-1, then decrease dose by 25%. Discontinue DOXIL if no resolution after 2 weeks.
Grade 4: Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization	<ul style="list-style-type: none"> Delay dosing up to 2 weeks or until resolved to Grade 0-1, then decrease dose by 25%. Discontinue DOXIL if no resolution after 2 weeks.
Stomatitis	
Grade 1: Painless ulcers, erythema, or mild soreness	<ul style="list-style-type: none"> If no previous Grade 3 or 4 toxicity: no dose adjustment. If previous Grade 3 or 4 toxicity: delay up to 2 weeks then decrease dose by 25%.
Grade 2: Painful erythema, edema, or ulcers, but can eat	<ul style="list-style-type: none"> Delay dosing up to 2 weeks or until resolved to Grade 0-1. Discontinue DOXIL if there is no resolution after 2 weeks. If resolved to Grade 0-1 within 2 weeks: <ul style="list-style-type: none"> <u>And</u> no previous Grade 3 or 4 stomatitis: resume treatment at previous dose. <u>And</u> previous Grade 3 or 4 toxicity: decrease dose by 25%.
Grade 3: Painful erythema, edema, or ulcers, and cannot eat	<ul style="list-style-type: none"> Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, discontinue DOXIL.
Grade 4: Requires parenteral or enteral support	<ul style="list-style-type: none"> Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, discontinue DOXIL.
Neutropenia or Thrombocytopenia	
Grade 1	No dose reduction
Grade 2	Delay until ANC \geq 1,500 and platelets \geq 75,000; resume treatment at previous dose
Grade 3	Delay until ANC \geq 1,500 and platelets \geq 75,000; resume treatment at previous dose
Grade 4	Delay until ANC \geq 1,500 and platelets \geq 75,000; resume at 25% dose reduction or continue previous dose with prophylactic granulocyte growth factor

Table 2: Recommended Dose Modifications of DOXIL for Toxicity When Administered in Combination With Bortezomib

Toxicity	DOXIL
Fever $\geq 38^{\circ}\text{C}$ and ANC $< 1,000/\text{mm}^3$	<ul style="list-style-type: none"> Withhold dose for this cycle if before Day 4; Decrease dose by 25%, if after Day 4 of previous cycle.
On any day of drug administration after Day 1 of each cycle: <ul style="list-style-type: none"> Platelet count $< 25,000/\text{mm}^3$ Hemoglobin $< 8 \text{ g/dL}$ ANC $< 500/\text{mm}^3$ 	<ul style="list-style-type: none"> Withhold dose for this cycle if before Day 4; Decrease dose by 25%, if after Day 4 of previous cycle AND if bortezomib is reduced for hematologic toxicity.
Grade 3 or 4 non-hematologic drug related toxicity	Do not dose until recovered to Grade < 2 , then reduce dose by 25%.

For neuropathic pain or peripheral neuropathy, no dosage adjustments are required for DOXIL. Refer to bortezomib manufacturer’s prescribing information.

2.6 Preparation and Administration

Preparation

Dilute DOXIL doses up to 90 mg in 250 mL of 5% Dextrose Injection, USP prior to administration. Dilute doses exceeding 90 mg in 500 mL of 5% Dextrose Injection, USP prior to administration. Refrigerate diluted DOXIL at 2°C to 8°C (36°F to 46°F) and administer within 24 hours.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Do not use with in-line filters.

Administer the first dose of DOXIL at an initial rate of 1 mg/min. If no infusion-related adverse reactions are observed, increase the infusion rate to complete the administration of the drug over one hour [see *Warnings and Precautions (5.2)*]. Do not rapidly flush the infusion line.

Do not mix DOXIL with other drugs.

Management of Suspected Extravasation

Discontinue DOXIL for burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Manage confirmed or suspected extravasation as follows:

- Do not remove the needle until attempts are made to aspirate extravasated fluid

- Do not flush the line
- Avoid applying pressure to the site
- Apply ice to the site intermittently for 15 min 4 times a day for 3 days
- If the extravasation is in an extremity, elevate the extremity

2.7 Procedure for Proper Handling and Disposal

Handle and dispose of DOXIL in accordance with recommendations for the handling and disposal of hazardous drugs.¹

If DOXIL comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

3 DOSAGE FORMS AND STRENGTHS

DOXIL: doxorubicin HCl liposomal injection: single use vials contain 20mg/10 mL and 50mg/25mL doxorubicin HCl as a translucent, red liposomal dispersion.

4 CONTRAINDICATIONS

DOXIL is contraindicated in patients who have a history of severe hypersensitivity reactions, including anaphylaxis, to doxorubicin HCl [*see Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Doxorubicin HCl can result in myocardial damage, including acute left ventricular failure. The risk of cardiomyopathy with doxorubicin HCl is generally proportional to the cumulative exposure. The relationship between cumulative DOXIL dose and the risk of cardiac toxicity has not been determined.

In a clinical study in 250 patients with advanced cancer who were treated with DOXIL, the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was between 450-550 mg/m². Cardiotoxicity was defined as >20% decrease in resting left ventricular ejection fraction (LVEF) from baseline where LVEF remained in the normal range or a >10% decrease in LVEF from baseline where LVEF was less than the institutional lower limit of normal. Two percent of patients developed signs and symptoms of congestive heart failure without documented evidence of cardiotoxicity.

Assess left ventricular cardiac function (e.g. MUGA or echocardiogram) prior to initiation of DOXIL, during treatment to detect acute changes, and after treatment to detect delayed cardiotoxicity. Administer DOXIL to patients with a history of cardiovascular disease only when the potential benefit of treatment outweighs the risk.

5.2 Infusion-Related Reactions

Serious and sometimes life-threatening infusion-related reactions characterized by one or more of the following symptoms can occur with DOXIL: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. The majority of infusion-related events occurred during the first infusion. Of 239 patients with ovarian cancer treated with DOXIL in Trial 4, 7% of patients experienced acute infusion-related reactions resulting in dose interruption. All occurred during cycle 1 and none during subsequent cycles. Across multiple studies of DOXIL monotherapy including this and other studies enrolling 760 patients with various solid tumors, 11% of patients had infusion-related reactions.

Ensure that medications to treat infusion-related reactions and cardiopulmonary resuscitative equipment is available for immediate use prior to initiation of DOXIL. Initiate DOXIL infusions at a rate of 1 mg/min and increase rate as tolerated [see *Dosage and Administration (2.6)*]. In the event of an infusion-related reaction, temporarily stop the drug until resolution then resume at a reduced infusion rate. Discontinue DOXIL infusion for serious or life-threatening infusion-related reactions.

5.3 Hand-Foot Syndrome (HFS)

In Trial 4, the incidence of HFS was 51% of patients in the DOXIL arm and 0.9% of patients in the topotecan arm, including 24% Grade 3 or 4 cases of HFS in DOXIL-treated patients and no Grade 3 or 4 cases in topotecan-treated patients. HFS or other skin toxicity required discontinuation of DOXIL in 4.2% of patients.

HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. Delay DOXIL for the first episode of Grade 2 or greater HFS [see *Dosage and Administration (2.5)*]. Discontinue DOXIL if HFS is severe and debilitating.

5.4 Secondary Oral Neoplasms

Secondary oral cancers, primarily squamous cell carcinoma, have been reported from post-marketing experience in patients with long-term (more than one year) exposure to DOXIL. These malignancies were diagnosed both during treatment with DOXIL and up to 6 years after the last dose. Examine patients at regular intervals for the presence of oral ulceration or with any oral discomfort that may be indicative of secondary oral cancer.

The altered pharmacokinetics and preferential tissue distribution of liposomal doxorubicin that contributes to enhanced skin toxicity and mucositis compared to free doxorubicin may play a role in the development of oral secondary malignancies with long-term use.

5.5 Embryofetal Toxicity

Based on animal data, DOXIL can cause fetal harm when administered to a pregnant woman. At doses approximately 0.12 times the recommended clinical dose, DOXIL was embryotoxic and abortifacient in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during and for 6 months after treatment with DOXIL [see *Use in Specific Populations (8.1) and (8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Cardiomyopathy [see *Warnings and Precautions (5.1)*]
- Infusion-Related Reactions [see *Warnings and Precautions (5.2)*]
- Hand-Foot Syndrome [see *Warnings and Precautions (5.3)*]
- Secondary Oral Neoplasms [see *Warnings and Precautions (5.4)*]

The most common adverse reactions (>20%) observed with DOXIL are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia.

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.

The safety data reflect exposure to DOXIL in 1310 patients including: 239 patients with ovarian cancer, 753 patients with AIDS-related Kaposi's sarcoma, and 318 patients with multiple myeloma.

The following tables present adverse reactions from clinical trials of single-agent DOXIL in ovarian cancer and AIDS-Related Kaposi's sarcoma.

Patients With Ovarian Cancer

The safety data described below are from Trial 4, which included 239 patients with ovarian cancer treated with DOXIL 50 mg/m² once every 4 weeks for a minimum of four courses in a randomized, multicenter, open-label study. In this trial, patients received DOXIL for a median number of 3.2 months (range 1 day to 25.8 months). The median age of the patients is 60 years (range 27 to 87), with 91% Caucasian, 6% Black, and 3% Hispanic or Other.

Table 3 presents the hematologic adverse reactions from Trial 4.

Table 3: Hematologic Adverse Reactions in Trial 4

	DOXIL Patients (n=239)	Topotecan Patients (n=235)
Neutropenia		
500 - <1000/mm ³	8%	14%
<500/mm ³	4.2%	62%
Anemia		
6.5 - <8 g/dL	5%	25%
< 6.5 g/dL	0.4%	4.3%
Thrombocytopenia		
10,000 - <50,000/mm ³	1.3%	17%
<10,000/mm ³	0.0%	17%

Table 4 presents the non-hematologic adverse reactions from Trial 4.

Table 4: Non-Hematologic Adverse Reactions in Trial 4

Non-Hematologic Adverse Reaction 10% or Greater	DOXIL (%) treated (n=239)		Topotecan (%) treated (n=235)	
	All grades	Grades 3-4	All grades	Grades 3-4
<i>Body as a Whole</i>				
Asthenia	40	7	52	8
Fever	21	0.8	31	6
Mucous Membrane Disorder	14	3.8	3.4	0
Back Pain	12	1.7	10	0.9
Infection	12	2.1	6	0.9
Headache	11	0.8	15	0
<i>Digestive</i>				
Nausea	46	5	63	8
Stomatitis	41	8	15	0.4
Vomiting	33	8	44	10
Diarrhea	21	2.5	35	4.2
Anorexia	20	2.5	22	1.3
Dyspepsia	12	0.8	14	0
<i>Nervous</i>				
Dizziness	4.2	0	10	0
<i>Respiratory</i>				
Pharyngitis	16	0	18	0.4
Dyspnea	15	4.1	23	4.3
Cough increased	10	0	12	0
<i>Skin and Appendages</i>				
Hand-foot syndrome	51	24	0.9	0
Rash	29	4.2	12	0.4
Alopecia	19	N/A	52	N/A

The following additional adverse reactions were observed in patients with ovarian cancer with doses administered every four weeks (Trial 4).

Incidence 1% to 10%

Cardiovascular: vasodilation, tachycardia, deep vein thrombosis, hypotension, cardiac arrest.

Digestive: oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus.

Hematologic and Lymphatic: ecchymosis.

Metabolic and Nutritional: dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia.

Nervous: somnolence, dizziness, depression.

Respiratory: rhinitis, pneumonia, sinusitis, epistaxis.

Skin and Appendages: pruritus, skin discoloration, vesicubullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne.

Special Senses: conjunctivitis, taste perversion, dry eyes.

Urinary: urinary tract infection, hematuria, vaginal moniliasis.

Patients With AIDS-Related Kaposi's Sarcoma

The safety data described is based on the experience reported in 753 patients with AIDS-related Kaposi's sarcoma (KS) enrolled in four open-label, uncontrolled trials of DOXIL administered at doses ranging from 10 to 40 mg/m² every 2 to 3 weeks. Demographics of the population were: median age 38.7 years (range 24-70); 99% male; 88% Caucasian, 6% Hispanic, 4% Black, and 2% Asian/other/unknown. The majority of patients were treated with 20 mg/m² of DOXIL every 2 to 3 weeks with a median exposure of 4.2 months (range 1 day to 26.6 months). The median cumulative dose was 120 mg/m² (range 3.3 to 798.6 mg/m²); 3% received cumulative doses of greater than 450 mg/m².

Disease characteristics were: 61% poor risk for KS tumor burden, 91% poor risk for immune system, and 47% poor risk for systemic illness; 36% were poor risk for all three categories; median CD4 count 21 cells/mm³ (51% less than 50 cells/mm³); mean absolute neutrophil count at study entry approximately 3,000 cells/mm³.

Of the 693 patients with concomitant medication information, 59% were on one or more antiretroviral medications [35% zidovudine (AZT), 21% didanosine (ddI), 16% zalcitabine (ddC), and 10% stavudine (D4T)]; 85% received PCP prophylaxis (54% sulfamethoxazole/trimethoprim); 85% received antifungal medications (76% fluconazole);

72% received antivirals (56% acyclovir, 29% ganciclovir, and 16% foscarnet) and 48% patients received colony-stimulating factors (sargramostim/filgrastim) during their course of treatment.

Adverse reactions led to discontinuation of treatment in 5% of patients with AIDS-related Kaposi's sarcoma and included myelosuppression, cardiac adverse reactions, infusion-related reactions, toxoplasmosis, HFS, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons. Tables 5 and 6 summarize adverse reactions reported in patients treated with DOXIL for AIDS-related Kaposi's sarcoma in a pooled analysis of the four trials.

Table 5: Hematologic Adverse Reactions Reported in Patients With AIDS-Related Kaposi's Sarcoma

	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n=74*)	Total Patients With AIDS-Related Kaposi's Sarcoma (n=720**)
Neutropenia		
< 1000/mm ³	46%	49%
< 500/mm ³	11%	13%
Anemia		
< 10 g/dL	58%	55%
< 8 g/dL	16%	18%
Thrombocytopenia		
< 150,000/mm ³	61%	61%
< 25,000/mm ³	1.4%	4.2%

*This includes a subset of subjects who were retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least 2 of 3 treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy.

**This includes only subjects with AIDS-KS who had available data from the 4 pooled trials.

Table 6: Non-Hematologic Adverse Reactions Reported in ≥ 5% of Patients With AIDS-Related Kaposi's Sarcoma

Adverse Reactions	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n=77*)	Total Patients With AIDS-Related Kaposi's Sarcoma (n=705**)
Nausea	18%	17%
Asthenia	7%	10%
Fever	8%	9%
Alopecia	9%	9%
Alkaline Phosphatase Increase	1.3%	8%
Vomiting	8%	8%
Diarrhea	5%	8%
Stomatitis	5%	7%
Oral Moniliasis	1.3%	6%

*This includes a subset of subjects who were retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least 2 of 3 treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy.

**This includes only subjects with AIDS-KS who had available adverse event data from the 4 pooled trials.

The following additional adverse reactions were observed in 705 patients with AIDS-related Kaposi's sarcoma.

Incidence 1% to 5%

Body as a Whole: headache, back pain, infection, allergic reaction, chills.

Cardiovascular: chest pain, hypotension, tachycardia.

Cutaneous: herpes simplex, rash, itching.

Digestive: mouth ulceration, anorexia, dysphagia.

Metabolic and Nutritional: SGPT increase, weight loss, hyperbilirubinemia.

Other: dyspnea, pneumonia, dizziness, somnolence.

Incidence Less Than 1%

Body As A Whole: sepsis, moniliasis, cryptococcosis.

Cardiovascular: thrombophlebitis, cardiomyopathy, palpitation, bundle branch block, congestive heart failure, heart arrest, thrombosis, ventricular arrhythmia.

Digestive: hepatitis.

Metabolic and Nutritional Disorders: dehydration

Respiratory: cough increase, pharyngitis.

Skin and Appendages: maculopapular rash, herpes zoster.

Special Senses: taste perversion, conjunctivitis.

Patients With Multiple Myeloma

The safety data described are from 318 patients treated with DOXIL (30 mg/m²) administered on day 4 following bortezomib (1.3 mg/m² i.v. bolus on days 1, 4, 8 and 11) every 3 weeks, in a randomized, open-label, multicenter study (Trial 6). In this trial, patients in the DOXIL + bortezomib combination group were treated for a median number of 4.5 months (range 21 days to 13.5 months). The population was 28 to 85 years of age (median age 61), 58% male, 90% Caucasian, 6% Black, and 4% Asian and Other. Table 7 lists adverse reactions reported in 10% or more of patients treated with DOXIL in combination with bortezomib for multiple myeloma.

Table 7: Frequency of Treatment-Emergent Adverse Reactions Reported in ≥10% Patients Treated for Multiple Myeloma With DOXIL in Combination With Bortezomib

Adverse Reaction	DOXIL + bortezomib (n=318)		Bortezomib (n=318)	
	Any (%)	Grade 3-4	Any (%)	Grade 3-4
Blood and lymphatic system disorders				
Neutropenia	36	32	22	16
Thrombocytopenia	33	24	28	17
Anemia	25	9	21	9
General disorders and administration site conditions				
Fatigue	36	7	28	3
Pyrexia	31	1	22	1
Asthenia	22	6	18	4
Gastrointestinal disorders				
Nausea	48	3	40	1
Diarrhea	46	7	39	5
Vomiting	32	4	22	1
Constipation	31	1	31	1
Mucositis/Stomatitis	20	2	5	<1
Abdominal pain	11	1	8	1
Infections and infestations				
Herpes zoster	11	2	9	2
Herpes simplex	10	0	6	1
Investigations				
Weight decreased	12	0	4	0
Metabolism and Nutritional disorders				
Anorexia	19	2	14	<1
Nervous system disorders				
Peripheral Neuropathy ¹	42	7	45	11
Neuralgia	17	3	20	4
Paresthesia/dysesthesia	13	<1	10	0
Respiratory, thoracic and mediastinal disorders				
Cough	18	0	12	0
Skin and subcutaneous tissue disorders				
Rash ²	22	1	18	1
Hand-foot syndrome	19	6	<1	0

¹ Peripheral neuropathy includes the following adverse reactions: peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, and neuropathy NOS.

² Rash includes the following adverse reactions: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, exfoliative rash, and rash generalized.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of DOXIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal and Connective Tissue Disorders: muscle spasms

Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism (in some cases fatal)

Hematologic disorders: Secondary acute myelogenous leukemia

Skin and subcutaneous tissue disorders: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Secondary oral neoplasms: [see Warnings and Precautions (5.4)].

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with DOXIL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, DOXIL can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, DOXIL was embryotoxic in rats and abortifacient in rabbits following intravenous administration during organogenesis at doses approximately 0.12 times the recommended clinical dose [see Data]. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

DOXIL was embryotoxic at doses of 1 mg/kg/day in rats and was embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about 0.12 times the recommended dose of 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.2 Lactation

Risk Summary

It is not known whether DOXIL is present in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue breastfeeding during treatment with DOXIL.

8.3 Females and Males of Reproductive Potential

Contraception

Females

DOXIL can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during and for 6 months after treatment with DOXIL.

Males

DOXIL may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and for 6 months after treatment with DOXIL [*see Nonclinical Toxicology (13.1)*].

Infertility

Females

In females of reproductive potential, DOXIL may cause infertility and result in amenorrhea. Premature menopause can occur with doxorubicin HCl. Recovery of menses and ovulation is related to age at treatment.

Males

DOXIL may result in oligospermia, azoospermia, and permanent loss of fertility. Sperm counts have been reported to return to normal levels in some men. This may occur several years after the end of therapy [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of DOXIL in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of DOXIL conducted in patients with either epithelial ovarian cancer (Trial 4) or with AIDS-related Kaposi's sarcoma (Trial 5) did not contain sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

In Trial 6, of 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Hepatic Impairment

The pharmacokinetics of DOXIL has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Reduce DOXIL for serum bilirubin of 1.2 mg/dL or higher.

10 OVERDOSAGE

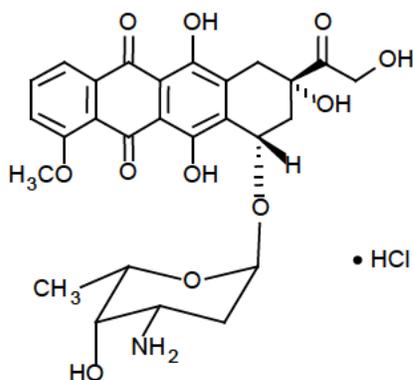
Acute overdosage with doxorubicin HCl causes increased risk of severe mucositis, leukopenia, and thrombocytopenia.

11 DESCRIPTION

DOXIL (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl), an anthracycline topoisomerase II inhibitor, that is encapsulated in STEALTH[®] liposomes for intravenous use.

The chemical name of doxorubicin HCl is (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxohexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The molecular formula is C₂₇H₂₉NO₁₁•HCl; its molecular weight is 579.99.

The molecular structure is:



DOXIL is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or

chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

12.3 Pharmacokinetics

The pharmacokinetic parameters for total doxorubicin following a single dose of DOXIL infused over 30 minutes are presented in Table 8.

Table 8: Pharmacokinetic Parameters of Total Doxorubicin from DOXIL in Patients With AIDS-Related Kaposi's Sarcoma

Parameter (units)	Dose	
	10 mg/m ²	20 mg/m ²
Peak Plasma Concentration (µg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m ²)	0.056 ± 0.01	0.041 ± 0.004
Steady State Volume of Distribution (L/m ²)	2.83 ± 0.145	2.72 ± 0.120
AUC (µg/mL•h)	277 ± 32.9	590 ± 58.7
First Phase (λ_1) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ_2) Half-Life (h)	52.3 ± 5.6	55.0 ± 4.8

N=23

Mean ± Standard Error

DOXIL displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Relative to DOXIL doses at or below 20 mg/m², the pharmacokinetics of total doxorubicin following a 50 mg/m² DOXIL dose are nonlinear. At this dose, the elimination half-life of DOXIL is longer and the clearance lower compared to a 20 mg/m² dose.

Distribution:

Direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5-10% free doxorubicin) remains liposome-encapsulated during circulation.

In contrast to doxorubicin, which displays a large volume of distribution (range 700 to 1100 L/m²), the small steady state volume of distribution of liposomal doxorubicin suggests that DOXIL is largely confined to vascular fluid. Doxorubicin becomes available after the liposomes are extravasated. Plasma protein binding of DOXIL has not been determined; the plasma protein binding of doxorubicin is approximately 70%.

Metabolism:

Doxorubicinol, the major metabolite of doxorubicin, was detected at concentrations of 0.8 to 26.2 ng/mL in the plasma of patients who received 10 or 20 mg/m² DOXIL.

Elimination:

The plasma clearance of total doxorubicin from DOXIL was 0.041 L/h/m² at a dose of 20 mg/m². Following administration of doxorubicin HCl, the plasma clearance of doxorubicin is 24 to 35 L/h/m².

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Mutagenicity or carcinogenicity studies have not been conducted with DOXIL, however doxorubicin was shown to be mutagenic in the *in vitro* Ames assay, and clastogenic in multiple *in vitro* assays (CHO cell, V79 hamster cell, human lymphoblast, and SCE assays) and the *in vivo* mouse micronucleus assay. The possible adverse effects on fertility in animals have not been adequately evaluated. DOXIL resulted in mild to moderate ovarian and testicular atrophy in mice after administration of a single dose of 36 mg/kg (about 2 times the 50 mg/m² human dose on a mg/m² basis). Decreased testicular weights and hypospermia were observed in rats after repeat doses \geq 0.25 mg/kg/day (about 0.03 times the 50 mg/m² human dose on a mg/m² basis), and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (about 0.4 times the 50 mg/m² human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

DOXIL was studied in three open-label, single-arm, clinical studies of 176 patients with metastatic ovarian cancer (Trials 1, 2, and 3). One hundred forty-five of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimens, defined as disease progression while on treatment or relapse within 6 months of completing treatment. Patients received DOXIL at 50 mg/m² every 3 or 4 weeks for 3-6+ cycles in the absence of dose-limiting toxicity or disease progression.

The median age at diagnosis ranged from 52 to 64 years in the 3 studies, and the range was 22 to 85. Most patients had International Federation of Obstetricians and Gynecologists (FIGO) stage III or IV disease (ranging from 83% to 93%). Approximately one third of the patients had three or more prior lines of therapy (ranging from 22% to 33%).

The primary outcome measure was confirmed response rate based on Southwestern Oncology Group (SWOG) criteria for patients refractory to both paclitaxel- and a platinum-containing regimen. Secondary efficacy parameters were time to response, duration of response, and time to progression.

The response rates for the individual single arm trials are given in Table 9 below.

Table 9: Response Rates in Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Trials

	Trial 1 (U.S.) N=27	Trial 2 (U.S.) N=82	Trial 3 (non-U.S.) N=36
Response Rate	22.2%	17.1%	0%
95% Confidence Interval	8.6% - 42.3%	9.7% - 27.0%	0.0% - 9.7%

In a pooled analysis of Trials 1-3, the response rate for all patients refractory to paclitaxel and platinum agents was 13.8% (95% CI 8.1% to 19.3%). The median time to progression was 15.9 weeks, the median time to response was 17.6 weeks, and the duration of response was 39.4 weeks.

In Trial 4, a randomized, multicenter, open-label, trial in 474 patients with epithelial ovarian cancer after platinum-based chemotherapy, patients were randomized to receive either DOXIL 50 mg/m² every 4 weeks (n=239) or topotecan 1.5 mg/m² daily for 5 consecutive days every 3 weeks (n=235). Patients were stratified according to platinum sensitivity (response to initial platinum-based therapy and a progression-free interval of greater than 6 months off treatment) and the presence of bulky disease (tumor mass greater than 5 cm in size). The primary outcome measure was time to progression (TTP). Other endpoints included overall survival and objective response rate.

Of the 474 patients, the median age at diagnosis was 60 years (range 25 to 87), 90% were FIGO stage III and IV; 46% were platinum sensitive; and 45% had bulky disease.

There was no statistically significant difference in TTP between the two arms. Results are provided in Table 10.

Table 10: Results of Efficacy Analyses¹

	Protocol Defined ITT Population	
	DOXIL (n=239)	Topotecan (n=235)
TTP (Protocol Specified Primary Endpoint)		
Median (Months) ²	4.1	4.2
p-value ³		0.62
Hazard Ratio ⁴		0.96
95% CI for Hazard Ratio		(0.76, 1.20)
Overall Survival		
Median (Months) ²	14.4	13.7
p-value ⁵		0.05
Hazard Ratio ⁴		0.82
95% CI for Hazard Ratio		(0.68, 1.00)
Response Rate		
Overall Response n (%)	47 (19.7)	40 (17.0)
Complete Response n (%)	9 (3.8)	11 (4.7)
Partial Response n (%)	38 (15.9)	29 (12.3)
Median Duration of Response (Months) ²	6.9	5.9

¹ Analysis based on investigators' strata for protocol defined ITT population.
² Kaplan-Meier estimates.
³ p-value is based on the stratified log-rank test.
⁴ Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for DOXIL.
⁵ p-value not adjusted for multiple comparisons.

14.2 AIDS-Related Kaposi's Sarcoma

DOXIL was studied in an open-label, single-arm, multicenter study at a dose of 20 mg/m² every 3 weeks, until disease progression or unacceptable toxicity (Trial 5).

Data is described for a cohort of 77 patients retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least two cycles of a regimen containing at least two of three treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy. Forty-nine of the 77 (64%) patients had received prior doxorubicin HCl.

The median time on study was 5.1 months (range 1 day to 15 months). The median cumulative dose of DOXIL was 154 mg/m² (range 20 to 620 mg/m²). Among the 77 patients, mean age was 38 years (range 24 to 54); 87% were Caucasian, 5% Hispanic, 4% Black, and 4% Asian/Other/Unknown; median CD4 count was 10 cells/mm³; ACTG staging criteria were 78% poor risk for tumor burden, 96% poor risk for immune system, and 58% poor risk for systemic illness at baseline; and mean Karnofsky status score was 74%. All patients had cutaneous or subcutaneous lesions, 40% also had oral lesions, 26% pulmonary lesions, and 14% had lesions of the stomach/intestine.

Two analyses of tumor response were used: one based on investigator assessment of changes in lesions based on modified ACTG criteria (partial response defined as no new lesions, sites of disease, or worsening edema; flattening of $\geq 50\%$ of previously raised lesions or area of indicator lesions decreasing by $\geq 50\%$; and response lasting at least 21 days with no prior progression), and one based on changes in up to five prospectively identified representative indicator lesions (partial response defined as flattening of $\geq 50\%$ of previously raised indicator lesions, or $>50\%$ decrease in the area of indicator lesions and lasting at least 21 days with no prior progression).

Of the 77 patients, 34 were evaluable for investigator assessment and 42 were evaluable for indicator lesion assessment; analyses of tumor responses are shown in Table 11.

Table 11: Response in Patients with Refractory¹ AIDS-Related Kaposi's Sarcoma

Investigator Assessment	All Evaluable Patients (n=34)	Evaluable Patients Who Received Prior Doxorubicin (n=20)
Response²		
Partial (PR)	27%	30%
Stable	29%	40%
Progression	44%	30%
Duration of PR (Days)		
Median	73	89
Range	42+ - 210+	42+ - 210+
Time to PR (Days)		
Median	43	53
Range	15 - 133	15 - 109
<hr/>		
Indicator Lesion Assessment	All Evaluable Patients (n=42)	Evaluable Patients Who Received Prior Doxorubicin (n=23)
Response²		
Partial (PR)	48%	52%
Stable	26%	30%
Progression	26%	17%
Duration of PR (Days)		
Median	71	79
Range	22+ - 210+	35 - 210+
Time to PR (Days)		
Median	22	48
Range	15 - 109	15 - 109

¹ Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

² There were no complete responses in this population.

Retrospective efficacy analyses were performed in two trials that had subsets of patients who received single-agent DOXIL and who were on stable antiretroviral therapy for at least 60 days prior to enrollment and until a response was demonstrated. In one trial, 7 of 17 (40%) patients had a durable response (median duration not reached but was longer than 11.6 months). In the second trial, 4 of 11 patients (40%) on a stable antiretroviral therapy demonstrated durable responses.

14.3 Multiple Myeloma

The efficacy of DOXIL in combination with bortezomib was evaluated in Trial 6, a randomized, open-label, international, multicenter study in 646 patients who had not previously received bortezomib and whose disease progressed during or after at least one prior therapy. Patients were randomized (1:1) to receive either DOXIL (30 mg/m²) administered IV on day 4 following bortezomib (1.3 mg/m² IV on days 1, 4, 8 and 11) or bortezomib alone every 3 weeks for up to 8 cycles or until disease progression or unacceptable toxicity. Patients who maintained a response were allowed to receive further treatment. The median number of cycles in each treatment arm was 5 (range 1-18).

The baseline demographics and clinical characteristics of the patients with multiple myeloma were similar between treatment arms (Table 12).

Table 12 Summary of Baseline Patient and Disease Characteristics

Patient Characteristics	DOXIL + bortezomib n=324	bortezomib n=322
Median age in years (range)	61 (28, 85)	62 (34, 88)
% Male/female	58 / 42	54 / 46
% Caucasian/Black/other	90 / 6 / 4	94 / 4 / 2%
Disease Characteristics		
% with IgG/IgA/Light chain	57 / 27 / 12	62 / 24 / 11
% β_2 -microglobulin group		
≤ 2.5 mg/L	14	14
> 2.5 mg/L and ≤ 5.5 mg/L	56	55
> 5.5 mg/L	30	31
Serum M-protein (g/dL): Median (Range)	2.5 (0-10.0)	2.7 (0-10.0)
Urine M-protein (mg/24 hours): Median (Range)	107 (0-24883)	66 (0-39657)
Median Months Since Diagnosis	35.2	37.5
% Prior Therapy		
One	34	34
More than one	66	66
Prior Systemic Therapies for Multiple Myeloma		
Corticosteroid (%)	99	>99
Anthracyclines	68	67
Alkylating agent (%)	92	90
Thalidomide/lenalidomide (%)	40	43
Stem cell transplantation (%)	57	54

The primary outcome measure was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease or death due to progressive disease. The combination arm demonstrated significant improvement in TTP. As the prespecified primary objective was achieved at the interim analysis, patients in the bortezomib monotherapy group were then allowed to receive the DOXIL + bortezomib combination. Survival continued to be followed after the interim analysis and survival data are not mature at this time. Efficacy results are as shown in Table 13 and Figure 1.

Table 13: Efficacy of DOXIL in Combination With Bortezomib in the Treatment of Patients With Multiple Myeloma

Endpoint	DOXIL + bortezomib n=324	Bortezomib n=322
Time to Progression¹		
Progression or death due to progression (n)	99	150
Censored (n)	225	172
Median in days (months)	282 (9.3)	197 (6.5)
95% CI	250;338	170;217
Hazard ratio ² (95% CI)		0.55 (0.43, 0.71)
p-value ³		<0.001
Response (n)⁴	303	310
% Complete Response (CR)	5	3
% Partial Response (PR)	43	40
% CR + PR	48	43
p-value ⁵		0.25
Median Duration of Response (months) (95% CI)	10.2 (10.2;12.9)	7.0 (5.9;8.3)

¹ Kaplan Meier estimate.

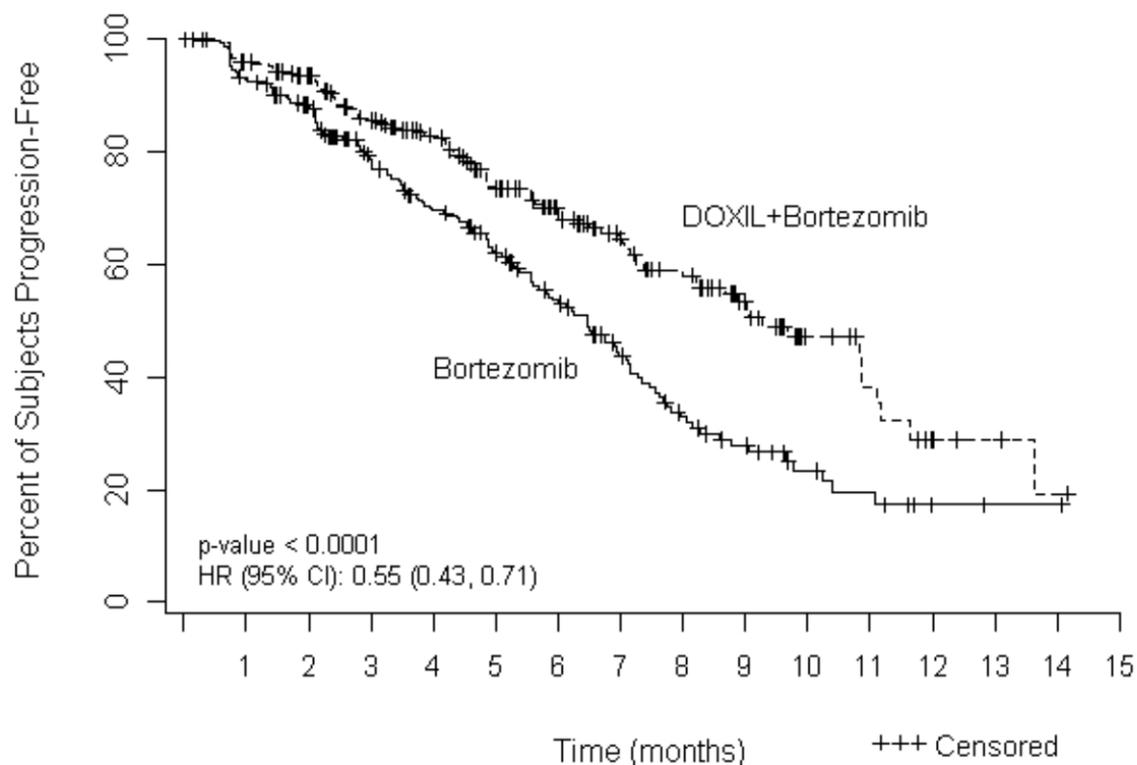
² Hazard ratio based on stratified Cox proportional hazards regression. A hazard ratio < 1 indicates an advantage for DOXIL+bortezomib.

³ Stratified log-rank test.

⁴ RR as per EBMT criteria.

⁵ Cochran-Mantel-Haenszel test adjusted for the stratification factors.

Figure 1- Time to Progression Kaplan-Meier Curve



Number of Subjects at Risk

DOXIL+Bortezomib	324	301	269	201	170	127	97	70	56	38	19	13	6	4	2	0
Bortezomib	322	290	253	189	150	112	84	56	35	25	14	9	2	1	1	0

15 REFERENCES

1. “Hazardous Drugs”, *OSHA*, <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

DOXIL is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials.

Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL.

Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL.

The following individually cartoned vials are available:

Table 14

mg in vial	fill volume	vial size	NDC #s
20 mg vial	10-mL	10-mL	59676-960-01
50 mg vial	25-mL	30-mL	59676-960-02

Refrigerate unopened vials of DOXIL at 2°- 8°C (36°- 46°F). Do not freeze.

Handle and dispose of DOXIL consistent with recommendations for the handling and disposal of hazardous drugs.¹

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

Advise patients to contact their healthcare provider if they develop symptoms of heart failure [see *Warnings and Precautions (5.1)*].

Infusion-Related Reactions

Advise patients about the symptoms of infusion related reactions and to seek immediate medical attention if they develop any of these symptoms [see *Warnings and Precautions (5.2)*].

Myelosuppression

Advise patients to contact their healthcare provider for a new onset fever or symptoms of infection.

Hand-Foot Syndrome

Advise patients to notify their healthcare provider if they experience tingling or burning, redness, flaking, bothersome swelling, small blisters, or small sores on the palms of their hands or soles of their feet (symptoms of Hand-Foot Syndrome) [see *Warnings and Precautions (5.3)*].

Stomatitis

Advise patients to notify their healthcare provider if they develop painful redness, swelling, or sores in the mouth (symptoms of stomatitis).

Embryofetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider with a known or suspected pregnancy [see *Warnings and Precautions (5.5) and Use in Specific Populations (8.1)*].

Advise females and males of reproductive potential to use effective contraception during and for 6 months following treatment with DOXIL [see *Use in Specific Populations (8.3)*].

Lactation

Advise females not to breastfeed during treatment with DOXIL [see *Use in Specific Populations (8.2)*].

Infertility

Advise females and males of reproductive potential that DOXIL may cause temporary or permanent infertility [see *Use in Specific Populations (8.3)*].

Discoloration of Urine and Body Fluids

Inform patients that following DOXIL administration, a reddish-orange color to the urine and other body fluids may be observed. This nontoxic reaction is due to the color of the product and will dissipate as the drug is eliminated from the body.

Manufactured by:
ALZA Corporation
Bedford, OH 44146

or

TTY Biopharm Company Limited
No. 838, Sec. 1, Chung Hwa Rd.
Chung-Li, Taoyuan, Taiwan, R.O.C.

Manufactured for:
Janssen Products, LP
Horsham, PA 19044
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Technology Product

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

OFFICE DIRECTOR MEMO

Division Director Summary Review

Date	November 11, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA Supplement #	NDA 50178/S-46
Applicant Name	Janssen Products, L.P.
Date of Submission	July 12, 2013
PDUFA Goal Date	November 12, 2013
Proprietary Name / Established (USAN) Name	Doxil/ doxorubicin HCl liposome injection
Dosage Forms / Strength	Single- (b) (4) vials for intravenous infusion/ 20 mg/10 mL and 50 mg/25 mL
Proposed Indication(s)	No new labeling claims
Action:	<i>Complete Response</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Anuja Patel
Medical Officer Review	Meredith Chuk
Pharmacology Toxicology Review	Shawn Weis
CMC Review	Kavita Vyas
Microbiology Review	Robert Mello
Biopharmaceutics Review	John Duan
Clinical Pharmacology Review	Safaa Burns
OPDP	Quynh-Van Tran
OSE/DMEPA	Otto Townsend

OND=Office of New Drugs
 CMC=-Chemistry Manufacturing and Controls
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

Division Director Summary Review

1. Introduction

This prior approval manufacturing supplement to the NDA for Doxil (doxorubicin HCl liposome injection; Janssen Products, L.P.) contains information intended to support the approval of:

- a new manufacturing site, TTY Biopharm Company Limited (TTY Biopharm) located in Chungli, Taoyuan, Taiwan, R.O.C. for the manufacturing process and (b) (4) operations of the drug product;
- a change in batch size of the drug product to (b) (4)
- a new (b) (4) stopper for the drug product;
- addition of a secondary packaging site at (b) (4) and
- a request for a waiver from the requirement to support the proposed manufacturing changes by conducting a bioequivalence (BE) study; the waiver is supported by results of a nonclinical bioequivalence assessment.

This supplement was managed by the Division of Oncology Products 2 because it contained non-clinical studies (bioequivalence assessment) and will require submission of the results of bioequivalence studies conducted in patients with solid tumors, with specific enrichment for patients with ovarian cancer, to support the approval of the new manufacturing site. The trial intended for this purpose, DOXILNAP1002 entitled, “A Pivotal Bioequivalence Study of DOXIL/CAELYX Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies including Subjects with Ovarian Cancer,” is ongoing.

A complete review of the application, as amended, has been performed and manufacturing inspections were conducted for this new facility. Deficiencies which preclude approval for this supplement are failure to provide adequate data on bioequivalence of drug product manufacturing at the new facility with the approved Doxil, lack of information on leachable/extractables with the new container closure components (b) (4) stopper), and insufficient information on the in vitro drug leakage assay and the in vitro drug release assay (leakage of doxorubicin from the liposome).

In addition, labeling changes are proposed for professional labeling (physician package insert) and carton/container labeling to remove to misleading statements, provide clarity to mitigate drug errors, and for conformance with current FDA Guidances and the Physician Labeling Rule.

2. Background

Regulatory history of NDA 50718

November 17, 1995: Original NDA approval granted under the provisions of 21 CFR 314 Subpart H (accelerated approval) for Doxil for the treatment of AIDS-related Kaposi's sarcoma (AIDS-KS) in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

June 28, 1999: approval under the provisions of 21 CFR 314 Subpart H (accelerated approval) for the treatment of refractory, advanced ovarian cancer.

October 27, 2004: Approval of efficacy supplement with clinical data to update the BOXED WARNINGS, WARNINGS, PRECAUTIONS (Information for the Patient), and DOSAGE AND ADMINISTRATION (AIDS-KS Patients, Dose Modifications and Preparation for Intravenous Administration) sections of product labeling based on results of a randomized, multicenter trial evaluating cardiac outcomes (clinical signs and symptoms of congestive heart failure) in patients receiving doxorubicin HCl or Doxil for the first-line treatment for metastatic breast cancer.

January 28, 2005: Approval granted for Doxil for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. This approval also fulfills the requirements under the provisions of 21 CFR 314 Subpart H (accelerated approval) for the June 28, 1999 accelerated approval for ovarian cancer.

May 17, 2007: Approval granted for Doxil, in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

June 10, 2008: Approval granted for Doxil for the treatment of AIDS-related Kaposi's Sarcoma after failure of prior systemic chemotherapy or intolerance to such therapy. This approval also fulfills the requirements under the provisions of 21 CFR 314 Subpart H (accelerated approval) for the November 17, 1995 accelerated approval for the treatment of AIDS-related Kaposi's sarcoma (AIDS-KS) in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

Regulatory history of N50718/S-046

DOXIL is a liposomal injectable formulation of doxorubicin hydrochloride (API) that is approved for commercial manufacture at Ben Venue Laboratories (BVL) in Bedford, OH.

This CMC prior approval supplement is one of multiple pending CMC supplements attempting to address drug shortages for Doxil based on serious deviations from Good Manufacturing Practices at BVL. Which is the only FDA-approved commercial manufacturing site.

Serious manufacturing issues at this facility were identified the

- Form FDA 483 issued on May 25, 2011 (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM275843.pdf>) and
- Form FDA 483 issued on December 2, 2011 (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM282550.pdf>).

On November 19, 2011, BVL proposed a voluntary shut down of manufacturing and distribution at its site in Bedford, Ohio due to significant manufacturing and quality concerns. (<http://www.fda.gov/drugs/drugsafety/ucm281782.htm>)

On January 31, 2013, FDA announced that a federal judge has approved a consent decree of permanent injunction against Ben Venue Laboratories, Inc., and three of its corporate officers for failing to comply with current Good Manufacturing Practice (GMP) requirements as required by federal law. (<http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm337561.htm>)

Against this background of persistent failure to comply with GMPs, Janssen has met with FDA on multiple occasions to discuss the data necessary to support new manufacturing sites. Discussions relating to need for human bioequivalence studies to support new manufacturing sites occurred on the following dates and methods of communication:

- January 13, 2012 Type A meeting to discuss Janssen's short-term and long-term plans to address GMP violations at BVL and maintain Doxil manufacturing and distribution.
- February 10, 2012: Janssen submitted a Protocol Element Document (PED) summarizing the design of a proposed bioequivalence (BE) study intended to support manufacturing changes involving a new manufacturing site.
- March 2, 2012, letter in which FDA provided comments on the proposed BE study, which included (1) a statement that AUC and Cmax for both free doxorubicin and liposome encapsulated doxorubicin should be obtained to determine the bioequivalence and (2) FDA agreed (b) (4)

[REDACTED] This latter agreement was retracted and Janssen was informed that the analysis of BE must be conducted in a patient population for which Doxil was indicated, based on FDA's recommendations for bioequivalence testing for doxorubicin HCl liposome injection products, found at (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf>)

- August 21, 2012 teleconference to discuss the proposed (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]. FDA requested Janssen submit the following: (1) a revised BE protocol to

allowing patients with any cancer to enroll to assess variability but that required the primary BE comparisons to be conducted in patients with ovarian cancer; (2) a statistical analysis plan for BE comparisons in a “to-be determined” minimum number of patients; (3) data and analyses from Phase 1 studies to address FDA’s concerns regarding comparability of pharmacokinetics (PK) across different cancer types to refute FDA’s argument that PK profile may be different; (4) all available data and references regarding free and encapsulated doxorubicin plasma concentrations to support the proposed approach; and (5) a description of the technical information available on assay methods and limitations.

- September 13, 2012: Janssen submitted a revised Protocol Element Document (PED) to establish BE based on encapsulated and unencapsulated (“free”) doxorubicin
- November 21, 2012 FDA letter regarding the revised BE study, noting that not all of the agreements made during the August 21, 2012 teleconference had been incorporated.
- December 11, 2012 teleconference: Discussion of Janssen’s response to the November 21, 2012 letter. Janssen stated that they did not agree with to include 24 ovarian cancer patients and to perform the definitive analysis of BE in patients with ovarian cancer. As discussed during the meeting and captured in FDA’s minutes “Janssen clarified that the current proposal would be for Stage 1 to include 24 patients (all comers, with 1/3 of those patients having ovarian cancer) and that the definitive analysis assessment be conducted in these 24 patients of encapsulated Doxil, noting that these data would then be used to calculate the sample size needed in Stage 2 for an assessment of free doxorubicin. FDA noted that a proposal that included a definitive analysis of 24 patients with ovarian cancer over Stage 1 and 2 would be acceptable. FDA declined to comment on the acceptability of the BE comparison at this time, but agreed to review and comment on the full BE protocol, particularly regarding the planned BE comparison of free doxorubicin, when the full protocol is submitted to IND 36778.” FDA also agreed that the December 5, 2012 submission containing the calculation formulae and criteria for determination of the sample size of pharmacokinetically-evaluable patients required for testing bioequivalence of free doxorubicin, based on the intra-patient variability of free doxorubicin across all patients enrolled in Stage 1 of the protocol was acceptable.
- April 25, 2013 e-mail communication to Janssen requesting submission of CMC information previously requested during the January 13, 2013 teleconference, In this e-mail, FDA requested the following (1) a comparison of the type of equipment to be used to manufacture Doxil at the proposed site and that used at the approved site and (2) Clarify whether this extended testing will be also be performed on Doxil manufactured at the TTY Biopharm Company Ltd, Taiwan site for the proposed BE study, as advised by FDA during the January 10, 2013 meeting and comments March 2, 2013 for the February 9, 2012 BE protocol submission, in regard to data needed to support approval of a new manufacturing site in Italy (BSP).
- May 24, 2013 e-mail communication to Janssen containing non-hold CMC comments regarding the revised Protocol DOXILNAP1002, submitted to IND 36778 on March 20,

2013. The CMC information requested to support review of this protocol were (1) data for the extended characterization studies performed on the batches made at proposed TTY facility and (2) data to support the suitability of the proposed stoppers for their intended use (for example, details of material of construction compared with approved stopper materials, and compatibility with Drug Product formulation including results of leachables and extractables study).

Submission History

- July 12, 2013: supplement submitted
- August 16, 2013: response to FDA's August 8, 2013 information request
- August 28, 2013: response to FDA's August 16, 2013 information request

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the chemistry reviewer regarding the deficiencies in the manufacturing of the drug product and drug substance, with regard to inadequate information on leachables/extractables for the new (b) (4) stoppers and lack of bioequivalence data, as requested prior to submission of this supplement in FDA's e-mail communication of April 25, 2013. Manufacturing site inspections were acceptable.

Dr. Vyas concluded that, based on the CMC information provided, the drug product manufactured at the new site in Taiwan is biochemically similar to that manufactured at the currently approved sites. No change in expiry dating was proposed. Stability studies are ongoing; Janssen submitted 6-month data real-time and accelerated stability data for (b) (4) batches to support the proposed expiry dating.

I also concur with the conclusions reached by the biopharmaceutics reviewer regarding the decision not to waive the requirement for bioequivalence studies in human subjects and that the data package submitted to support a request for waiver, based on product characterization and non-clinical studies, is inadequate. In addition, additional data were needed on the in vitro drug leakage assay of doxorubicin from the encapsulated liposome and on the in vitro drug release assay, as discussed in FDA's recommendations on bioequivalence assessment of doxorubicin HCl liposome drug products.

The outstanding issues that preclude approval are

- inadequate data on bioequivalence of drug product manufacturing at the new facility with the approved Doxil;
- lack of information on leachable/extractables with the new container closure components (a (b) (4) stopper), and
- insufficient information on the in vitro drug leakage assay; and
- insufficient information on the in vitro drug release assay.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The supplement contained the results of bioequivalence studies in rats and mice comparing pharmacokinetics, tissue distribution, and “efficacy” between drug product manufactured at the approved manufacturing site (Bedford OH) with that manufactured at the proposed new facility. The clinical pharmacology reviewer concluded that the overall pharmacokinetic profile was similar did not meet consistently the clinical bioequivalence criteria (90% CI 80 to 125) for AUC for either total (encapsulated plus free) or free doxorubicin and in some instances were based on routes of administration (intravenous bolus) which are not recommended for human use. In addition, the two drug products were not similar for tissue distribution characteristics. While the clinical pharmacology reviewer stated that “as tissue distribution is not typically assessed for the purposes of bioequivalence testing, the relevance of this observation to the question of bioequivalence is unclear,” I note that the importance of tissue distribution to the mechanism of action of Doxil is described in product labeling. Specifically, product labeling states

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated DOXIL liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the STEALTH liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl becomes available.

The pharmacology/toxicology reviewer concluded that the nonclinical bioequivalence assessment data demonstrate bioequivalence in animals, however these conclusions cannot be extrapolated to, or support a conclusion of bioequivalence in, human subjects

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. No new clinical pharmacology data were provided in this supplement. Modifications to the package insert for consistency with the Physician Labeling Rule and FDA Guidances for product labeling were proposed by the Clinical Pharmacology reviewer in conjunction with other review team members.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval. Manufacturing changes and procedures conform to industry standards and FDA Guidances. The safety of the proposed storage conditions for the diluted product (up to 24 hours under refrigerated conditions) is adequately supported.

7. Clinical/Statistical-Efficacy

Not applicable

8. Safety

Not applicable

9. Advisory Committee Meeting

Not applicable for this manufacturing supplement.

10. Pediatrics

This CMC supplement is not subject to the requirements of PREA because it does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Not applicable for this manufacturing supplement; no proposed change in the proprietary name.
- Physician labeling; major issues that were not discussed with Janssen Product, L.P. during the manufacturing supplement review and that will be addressed during review of the resubmission include

- updates to the Boxed Warnings, Warnings and Precautions, Contraindications, Dosage and Administration, and Overdosage sections to conform with the requirements of the Physicians Labeling Rule content and format and FDA Guidance for Industry for these sections of product labeling
- Recommendations for updates to the Use in Specific Populations section to conform to current recommendations for this section as communicated by the Pediatric and Maternal Health Team.
- Recommendations to other sections of the label based on the requirements of the Physicians Labeling Rule content and format and FDA Guidance for Industry for these sections of product labeling.

Preliminary comments on Physician labeling will be conveyed as an attachment to the Complete Response letter

- Carton and immediate container labels: Comments from DMEPA to ensure carton and immediate container labels conform to applicable FDA Guidances and regulations and to remove misleading or unnecessary statements will be conveyed to Janssen.
- Patient labeling/Medication guide: Not applicable. There is no patient labeling for Doxil.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response

- Risk Benefit Assessment

Insufficient information has been provided to ensure that the product manufactured at the new site (TTY) is sufficiently similar to the product currently marketed to permit approval. The pending manufacturing issues require submission of additional information requested prior to submission of the efficacy supplement or described in specific recommendations for this product on FDA's public website. The need for bioequivalence studies in human subjects is discussed in FDA's recommendations for bioequivalence testing for doxorubicin HCl liposome injection products, found at (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf>). This requirement discusses locally acting products with complex bioequivalence requirements. The recommendations are that single dose fasting two-way crossover bioequivalence studies be conducted in ovarian cancer patients at 50 mg/m² dose. This recommendation is consistent with the SUPAC-MR guidance. As noted by the biopharmaceutics team, although this guidance was intended for modified release oral dosage forms, the same general concepts apply to non-oral modified release dosage forms, such as liposomal products, which are complex modified release delivery systems.

Alternatively, Janssen may provide additional data to support a request for a waiver from the requirement to conduct a BE study, specifically by demonstration of robust results in an In-vitro In-vivo Correlation (IVIVC) model for Doxil in which IVIVC is

confirmed. While this approach could be appropriate, this approach is not recommended because Janssen has already failed to establish IVIVC and any assessment of the robustness of the new IVIVC model must include a consideration of the previous results.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**
Based on review of this supplement to date, a REMS is not required to ensure safe use of this product.
- **Recommendation for other Postmarketing Requirements and Commitments**
Based on review of this supplement to day, there are no recommendations for post-marketing requirements or commitments. A final determination on the need for post-marketing requirements or commitments will be made at the time of a final action resulting in approval.

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/s/

PATRICIA KEEGAN
11/11/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

MEDICAL REVIEW(S)

NDA 50718
SDN(s): 926, 943, 947, 948
SUBMIT DATE(S): September 22, 2014 (SDN 926); January 9, 2015 (SDN 943); January 16, 2015 (SDN 947); January 19, 2015 (SDN 948)
PRODUCT: Doxil (doxorubicin HCl liposome injection)
APPLICANT: Janssen Products, LP
PDUFA DATE: January 22, 2015
CLINICAL REVIEWER Meredith K. Chuk
CLINICAL TEAM LEADER Marc Theoret

CLINIAL REVIEW EXECUTIVE SUMMARY:

NDA050718-S46 is a CMC supplement for a new manufacturing site for Doxil and includes the results of a bioequivalence (BE) study and updated product labeling. This review focuses on the safety information provided in the clinical study report (CSR) and datasets for the BE study and major changes to the product labeling made in accordance with the January 24, 2006, Final Rule on “*Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*”.

This reviewer did not identify any major safety concerns or new safety signals in this clinical trial with the use of either the test or reference Doxil product. The adverse events reported in the trial were consistent with the known safety profile of Doxil.

Major changes to the product labeling were:

- Deletion of the following adverse events from the box warning for inadequate data on the severity of these reactions to support their inclusion: severe myelosuppression, dose reduction in patients with impaired hepatic function, and accidental substitution
- Deletion of myelosuppression from the Warnings and Precautions section given lack of data on the seriousness of this adverse reaction

Please see review by Okpo Eradiri, Ph.D., FDA Biopharmaceutics Reviewer for details regarding the pharmacokinetic results of the BE study and modifications of the data analysis requirements made during the course of the study to reflect the very low systemic exposure of free doxorubicin. Please see review by Kavita A. Vyas, Ph.D., FDA Chemistry reviewer for details on the chemistry portion of the supplement.

BACKGROUND:

On September 22, 2014, Janssen submitted CMC Supplement 46 to NDA 050718 for a new manufacturing site, TTY Biopharm Company Limited (TTY Biopharm) located in Chungli, Taoyuan, Taiwan, R.O.C. for the manufacturing process, [REDACTED] (b) (4) operations of the drug product. With this supplement Janssen also submitted revised product labeling. This submission was a response to a Complete Response letter issued by the FDA on July 12, 2013, in which the Agency stated that the bioequivalence (BE) waiver request that Janssen submitted was not acceptable and that a BE study is required.

SAFETY REVIEW:

Study Design

NDA050718-S46 contains a CSR for the BE study “A Pivotal Bioequivalence Study of DOXIL®/CAELYX® Manufactured at a New Site in Subjects With Advanced or Refractory Solid Malignancies Including Subjects With Ovarian Cancer.” The trial was a randomized, open-label, single-center, single-dose, 2-cycle, crossover study in subjects with refractory malignancies, including ovarian cancer. The primary objective of the trial was to investigate the bioequivalence of Doxil manufactured at a new site (TTY Biopharm Company Limited in Chungli, Taoyuan, Taiwan), and at a currently approved site (Ben Venue Laboratories, Bedford, Ohio, US). Secondary objectives included the safety of Doxil and the investigator-determined response at the end-of-treatment visit.

The study included a Screening Phase followed by an open-label Treatment Phase consisting of two Doxil treatment cycles (28-days each), one cycle with each Treatment, A and B:

- Treatment A consisted of doxorubicin HCl liposome injection [Doxil] produced at the current manufacturing site (Ben Venue Laboratories, Bedford, Ohio, US= reference product) administered by intravenous (IV) infusion over 90 minutes at a dose of 50 mg/m²
- Treatment B consisted of doxorubicin HCl liposome injection produced at a new manufacturing site (TTY Biopharm Co., Chungli Taoyuan, Taiwan= test product) administered by IV infusion over 90 minutes at a dose of 50 mg/m²

Patients were randomized (1:1) to one of two treatment sequence groups, Sequence AB or BA. Randomization was stratified by ovarian cancer versus non-ovarian cancer patients. Following the Treatment Phase, subjects could then enter the optional Extension Phase to continue to receive the reference Doxil for up to one year in the absence of disease progression or unacceptable toxicity.

Blood samples for pharmacokinetic studies of free and encapsulated doxorubicin were to be obtained at specified times over 29 days in Cycles 1 and 2. The initial study plan consisted of an adaptive analysis with at least 24 patients with ovarian cancer for determination of bioequivalence based on encapsulated doxorubicin. An agreement was reached with FDA during the course of the trial during a teleconference on April 14, 2014 (meeting minutes under IND36778 issued May 14, 2014), to include patients with all cancer types in the primary analysis of bioequivalence given existing data provided by Janssen and reviewed by FDA Biopharmaceutics reviewers that the pharmacokinetics of doxorubicin were similar between patients with ovarian cancer and other tumor types.

Results

The trial was initiated on May 30, 2013, and the clinical data cutoff was April 28, 2014. Fifty-four patients were randomized and data from 52 patients (24 with ovarian cancer and 28 with other solid tumors) are included in the CSR (two patients had not completed 2 cycles of treatment at the time of data cut-off). Of the 52 patients, 46 completed the treatment phase, five discontinued treatment early (AE of bone marrow failure, withdrawal of consent, and progressive disease, n=1 each and reason “other” n=2), and one never received study drug.

Fifty-one patients received at least one dose of study medication and are included in the safety review. No adverse events leading to death were reported in either group. One patient died on study in Sequence BA

of progressive disease. One patient had an adverse event of bone marrow failure in Sequence AB that led to study drug discontinuation. Six patients receiving Treatment A (reference product) and seven patients receiving Treatment B (test product) had treatment delays following cycle 1. Two patients had dose reductions in cycle 2 for toxicity (Treatment A= stomatitis; Treatment B=neutropenia). Serious adverse events (SAEs) were reported for 12 (24%) of patients. SAEs reported in more than 1 patient included pulmonary embolism (n=2 in Treatment A and n=1 in Treatment B), and abdominal pain (n=2 in Treatment A). Table 1 summarizes the SAEs reported in the trial.

Table 1: Serious Adverse Events

Table 19: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study DOXILNAP1002)

	All Cancer Types		Total
	Trt B ^a	Trt A ^a	
Analysis set: safety subjects	49	50	51
Number of subjects with serious TEAEs	5 (10.2%)	8 (16.0%)	12 (23.5%)
System Organ Class			
Preferred Term			
Gastrointestinal disorders	2 (4.1%)	3 (6.0%)	5 (9.8%)
Abdominal pain	0	2 (4.0%)	2 (3.9%)
Abdominal distension	0	1 (2.0%)	1 (2.0%)
Abdominal pain upper	1 (2.0%)	0	1 (2.0%)
Intestinal obstruction	0	1 (2.0%)	1 (2.0%)
Stomatitis	1 (2.0%)	0	1 (2.0%)
Vomiting	0	1 (2.0%)	1 (2.0%)
Respiratory, thoracic and mediastinal disorders	1 (2.0%)	2 (4.0%)	3 (5.9%)
Pulmonary embolism	1 (2.0%)	2 (4.0%)	3 (5.9%)
General disorders and administration site conditions	1 (2.0%)	0	1 (2.0%)
Pyrexia	1 (2.0%)	0	1 (2.0%)
Hepatobiliary disorders	1 (2.0%)	0	1 (2.0%)
Hyperbilirubinaemia	1 (2.0%)	0	1 (2.0%)
Infections and infestations	0	1 (2.0%)	1 (2.0%)
Pneumonia	0	1 (2.0%)	1 (2.0%)
Musculoskeletal and connective tissue disorders	0	1 (2.0%)	1 (2.0%)
Back pain	0	1 (2.0%)	1 (2.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (2.0%)	1 (2.0%)
Metastases to central nervous system	0	1 (2.0%)	1 (2.0%)
Reproductive system and breast disorders	0	1 (2.0%)	1 (2.0%)
Metrorrhagia	0	1 (2.0%)	1 (2.0%)
Skin and subcutaneous tissue disorders	1 (2.0%)	0	1 (2.0%)
Palmar-plantar erythrodysesthesia syndrome	1 (2.0%)	0	1 (2.0%)
Vascular disorders	0	1 (2.0%)	1 (2.0%)
Deep vein thrombosis	0	1 (2.0%)	1 (2.0%)

^a A: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at current site (BVL); B: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at new site (TTY).

Note: A subject was counted once within each system organ class, preferred term and treatment. Adverse Events were coded using MedDRA Version 16.1.

[TSFAE06A.rtf] [JNJ-17302753\NAP1002\DBR_STAGE1\RE_CSR\tsfae06a.sas] 21JUL2014, 17:28

Source: CSR DOXILNAP1002; verified with AE xpt, ADAE.xpt

The most commonly reported (>10%) treatment-emergent AEs in all patients were fatigue (43%), nausea (35%), neutropenia (33%), stomatitis (31%), vomiting (24%), anemia (22%), asthenia (20%), constipation (20%), HFS (18%), decreased appetite (18%), palmar-plantar erythrodysesthesia syndrome (18%), hepatic function abnormal (14%), and diarrhea (12%).

As shown in Table 2, treatment-emergent AEs were similar in patients following either Treatment A or B, with the exception of hepatic function abnormalities which were reported in 12% of patients following Treatment B and 4% following Treatment A; however, the laboratory abnormalities following both

treatments were generally low grade and no patient had Grade 3 or 4 increases in ALT, AST, or bilirubin following Treatment B.

Table 2: Adverse Events ≥10%

Table 18: Treatment-emergent Adverse Events by System Organ Class and Preferred Term: TEAEs reported for ≥10% of Total Subjects; Safety Analysis Set (Study DOXILNAP1002)	All Cancer Types		
	Trt B ^a	Trt A ^a	Total
Analysis set: safety subjects	49	50	51
Number of subjects with TEAE	43 (87.8%)	46 (92.0%)	50 (98.0%)
System Organ Class			
Preferred Term			
Gastrointestinal disorders	25 (51.0%)	31 (62.0%)	39 (76.5%)
Nausea	13 (26.5%)	10 (20.0%)	18 (35.3%)
Stomatitis	12 (24.5%)	9 (18.0%)	16 (31.4%)
Vomiting	6 (12.2%)	8 (16.0%)	12 (23.5%)
Constipation	4 (8.2%)	7 (14.0%)	10 (19.6%)
Diarrhoea	4 (8.2%)	3 (6.0%)	6 (11.8%)
General disorders and administration site conditions	26 (53.1%)	20 (40.0%)	36 (70.6%)
Fatigue	16 (32.7%)	13 (26.0%)	22 (43.1%)
Asthenia	4 (8.2%)	7 (14.0%)	10 (19.6%)
Blood and lymphatic system disorders	17 (34.7%)	19 (38.0%)	23 (45.1%)
Neutropenia	12 (24.5%)	14 (28.0%)	17 (33.3%)
Anaemia	6 (12.2%)	10 (20.0%)	11 (21.6%)
Skin and subcutaneous tissue disorders	12 (24.5%)	12 (24.0%)	21 (41.2%)
Palmar-plantar erythrodysesthesia syndrome	5 (10.2%)	5 (10.0%)	9 (17.6%)
Metabolism and nutrition disorders	6 (12.2%)	12 (24.0%)	13 (25.5%)
Decreased appetite	3 (6.1%)	7 (14.0%)	9 (17.6%)
Hepatobiliary disorders	6 (12.2%)	2 (4.0%)	7 (13.7%)
Hepatic function abnormal	6 (12.2%)	2 (4.0%)	7 (13.7%)

^a A: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at current site (BVL); B: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at new site (TTY).

Note: A subject was counted once within each system organ class, preferred term and treatment. Adverse Events were coded using MedDRA Version 16.1.

Source: adapted from TSFAE02A.rtf

Source: CSR DOXILNAP1002; verified with AE xpt, ADAE.xpt

LABELING REVIEW:

See Table 3 for a brief review of major labeling changes. Edits were made for clarity, brevity, consistency, and active voice, and revisions were made in formatting in accordance with PLR guidelines throughout the label.

Table 3: Labeling Review

LABELING REVIEW	
HIGHLIGHTS OF PRESCRIBING INFORMATION	<ul style="list-style-type: none"> Edits were made for consistency with rest of label.
FULL PRESCRIBING INFORMATION	
BOX WARNING	<ul style="list-style-type: none"> “Myelosuppression”, “dose reduction for hepatic impairment”, and “accidental substitution” deleted as they did not reach the level of severity to be included in the box warning.
1. INDICATIONS AND USAGE	<ul style="list-style-type: none"> No major changes
2. DOSAGE AND ADMINISTRATION	<ul style="list-style-type: none"> Section on <i>Patients with Impaired Hepatic Function</i> (formally Section 2.6) was deleted given lack of data with Doxil to support recommendations. Recommendations for dose adjustments for bortezomib were deleted and prescribers are referred to bortezomib label for dose modifications.
3. DOSAGE FORMS AND STRENGTHS	<ul style="list-style-type: none"> No major changes
4. CONTRAINDICATIONS	<ul style="list-style-type: none"> Modified to remove reference to patients with a history of hypersensitivity reactions to the components of Doxil as the Applicant could not provide data to support this as a known hazard.

<p>5. WARNINGS AND PRECAUTIONS</p>	<ul style="list-style-type: none"> • Section on <i>Cardiac toxicity</i> was renamed to <i>Cardiomyopathy</i> to more accurately reflect the risk and section was revised to reflect recent relevant changes to doxorubicin label. • Section on <i>Infusion reactions</i> was renamed to <i>Infusion-related reactions</i> and updated with clinical data to give additional information to prescribers and to support dose-modification guidelines. • Section on <i>Myelosuppression</i> deleted as the severity of the adverse reaction did not warrant inclusion in Warnings and Precautions section. • Section on <i>Hand-Foot Syndrome</i> was condensed by limiting description to the appropriate data from clinical trials that support its inclusion in this Section. • Section on <i>Radiation Recall</i> was deleted given lack of data for appropriate inclusion in this section. • Section formally entitled <i>Fetal Mortality</i> was renamed <i>Embryofetal Toxicity</i>, content was revised, and pregnancy category was removed in accordance with new FDA labeling guidelines. • Sections on <i>Toxicity Potentiation</i> and <i>Monitoring: Laboratory Tests</i> deleted by Sponsor as content was relocated to other sections. The Clinical Reviewer agrees with deletion of these sections and reviewed the text in the context of its new location
<p>6. ADVERSE REACTIONS</p>	<ul style="list-style-type: none"> • Section was updated with additional descriptive information about the clinical studies for more informative labeling consistent with current labeling Guidances. • Adverse reaction tables modified to round incidences 5% or greater to the nearest whole number consistent with current labeling practices
<p>7. DRUG INTERACTIONS</p>	<ul style="list-style-type: none"> • No major changes
<p>8. USE IN SPECIFIC POPULATIONS</p>	<ul style="list-style-type: none"> • Sections added, renamed, and reordered consistent with the Pregnancy and Lactation Labeling Rule <ul style="list-style-type: none"> • Section 8.3 <i>Nursing Mothers</i> revised to Section 8.2 <i>Lactation</i> • Section 8.3 <i>Females and Males of Reproductive Potential</i> was added in accordance with recent FDA labeling guidelines. • Section on <i>Geriatric Use</i> was updated in accordance with current FDA labeling guidelines.
<p>10. OVERDOSAGE</p>	<ul style="list-style-type: none"> • No major changes
<p>11. DESCRIPTION</p>	<ul style="list-style-type: none"> • No major changes. See FDA CMC Review for details.

12. CLINICAL PHARMACOLOGY	<ul style="list-style-type: none"> No major changes; however, section was heavily edited for brevity and essential information. See FDA Clinical Pharmacology labeling review for further details.
13. NONCLINICAL TOXICOLOGY	<ul style="list-style-type: none"> Revisions were made in formatting in accordance with PLR guidelines by the FDA Pharmacology/Toxicology reviewer.
14. CLINICAL STUDIES	<ul style="list-style-type: none"> No major changes but section was heavily edited for brevity and essential information.
15. REFERENCES	<ul style="list-style-type: none"> Revised per PLR guidance and only OSHA Hazardous Drugs references are included.
16. HOW SUPPLIED/STORAGE AND HANDLING	<ul style="list-style-type: none"> No major changes
17. PATIENT COUNSELING INFORMATION	<ul style="list-style-type: none"> Revisions were made for consistency with remainder of the label.

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/s/

MEREDITH K CHUK
01/22/2015

MARC R THEORET
01/22/2015

Clinical Review of NDA Supplement**NDA:** 50718**SDN:** 883**Drug:** Doxil**Sponsor:** Janssen Products, LP**Date submitted:** 7/12/13**Reviewer:** Meredith Chuk**Team Leader:** Marc Theoret

On July 12, 2013, Janssen Products, LP submitted Supplement 46 (SDN 883) to NDA 50718, a CMC supplement for the manufacture of Doxil at an additional facility, TTY Biopharm located in Taiwan. The submission contained CMC and non-clinical information and a request for waivers for in vivo studies [bioequivalence study waiver request].

Supplement 46 contained no clinical information for review; however, the clinical team and Ann Marie Trentacosti of the SEALD team provided general comments to Janssen for guidance in updating the prescribing information (PI) with their next submission in accordance with the January 24, 2006, Final Rule on *“Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products”*.

Comments were also provided on the following sections of the Doxil PI that were impacted by the PLR conversion of the PI for doxorubicin, which FDA approved on October 31, 2013 [NDA 50629 (Supplement 22) and 50467 (Supplement 73)]:

- Boxed Warning
- Section 2.6 Patients With Impaired Hepatic Function
- Section 5.1 Cardiac Toxicity
- Section 5.6 Embryofetal Toxicity
- 8.6 Females and Males of Reproductive Potential

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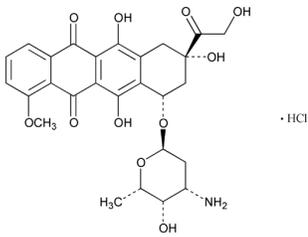
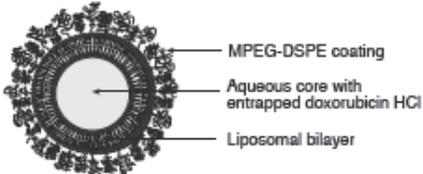
MEREDITH K CHUK
11/06/2013

MARC R THEORET
11/07/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

CHEMISTRY REVIEW(S)

Chemistry Review: # 1	1. Division: DOP1	2. NDA Number: 50-718
3. Name and Address of Applicant: Janssen Products, LP, Janssen Research & Dev 920 Route 202 South, P.O. Box 300, Raritan NJ 08869 On behalf of Janssen Products., LP, 430 Rt 22 E, PO Box 69, Bridgewater, NJ 08807		4. Supplement(s): Number: 046 Date(s): 7/12/2013
5. Name of Drug: DOXIL	6. Nonproprietary name: Doxorubicin HCl Liposome Injection	
7. Supplement Provides for: additional facility, TTY Biopharm, Taiwan, for the manufacture of Doxil.		8. Amendment(s):
9. Pharmacological Category: Antineoplastic	10. How Dispensed: R _x	11. Related Documents: (b) (4) IND 36778 (amendment 3/20/2012)
12. Dosage Form: Injection	13. Potency: 2mg/mL	
14. Chemical Name and Structure: Doxorubicin encapsulated in Liposomes. (8 <i>S</i> ,10 <i>S</i>)-10-[(3-Amino-2,3,6-trideoxy- β -L- <i>lyxo</i> -hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.		
<div style="text-align: center;">  <p>· HCl</p> </div> <p style="text-align: center;">Representation of a STEALTH[®] liposome:</p> <div style="text-align: center;">  <p>— MPEG-DSPE coating — Aqueous core with entrapped doxorubicin HCl — Liposomal bilayer</p> </div>		
15. Comments: This PAS provides for the addition of a new site for the manufacture of DP (TTY Biopharm, Taiwan). No mention of changes to formulation, the process, or methods is made. The following changes are also proposed (i) Change in batch size of DP – from (b) (4) (at BVL/ (b) (4)) to (b) (4) at the proposed facility. (ii) Minor changes in process resulting from changes in equipment at the new site. (iii) Change in the specification for DP containers and closures – (b) (4) Stoppers. (iv) Addition of a secondary packaging site: (b) (4) (v) Addition of nonclinical data in labeling. (vi) BE study waiver.		
<p>In support, the applicant provided (i) Comparative batch and stability data for (b) (4) batches manufactured at TTY and BVL (b) (4) (ii) Extended characterization data for (b) (4) TTY batches and (b) (4) batches from BVL (requested by the Agency during 1/2012 meeting with the applicant). (iii) Validation of the sterilization process. (iv) Nonclinical results of testing of TTY batches. Not evaluated here.</p> <p>The CMC data examined (except in vitro release data) indicate that DP made at TTY and BVL (b) (4) appear comparable based on the release data, stability data, and on extended characterization data that are necessary for this liposomal formulation. However, the applicant did not</p>		

<p>provide leachables/extractables data for the proposed (b) (4) stoppers. <i>In vitro</i> release data, f2 comparison, and the request for biowaiver were not examined here. Biopharm reviewer recommends a Complete Response from a Biopharm perspective (see review by Dr. John Duan dated 9/19/13). Microbiology reviewer recommends Approval from Microbiology point of view (see review by Dr. Robert Mello dated 8/29/13). The OC recommends the proposed site as Acceptable based District recommendation (11/3/13).</p>			
<p>16. Conclusion: Recommend Complete Response for NDA 50-718 S-046 from a CMC point of view based on Biopharm recommendation.</p>			
<p>17. Name: Kavita A. Vyas, Ph.D., Chemist</p>	<p>Signature:</p>	<p>Date: 10/25/2013</p>	
<p>18. Concurrence: Hasmukh Patel, Ph.D., Branch Chief, Div., III, ONDQA</p>	<p>Signature:</p>	<p>Date:</p>	

Background Information

NDA 50-718 was approved in November 1995 for the treatment of Kaposi's Sarcoma in certain AIDS patients. DP is doxorubicin encapsulated in long-circulating STEALTH liposomes. The latter are microscopic vesicles composed of phospholipid bilayer, formulated with surface bound methoxypolyethylene glycol (MPEG).

The Agency and Janssen have worked since 2012 to resolve Doxil shortage. Janssen proposed (b) (4) a long term strategy to transfer the Doxil manufacturing process to (b) (4) in January 2012. The Agency advised Janssen that extended physicochemical testing, and bioequivalence clinical trials, will be necessary to demonstrate the comparability of DP made at the proposed and approved sites due to the nature of this DP, together with a list of tests required (see meeting minutes dated 1/10/2012 and 2/9/2012 for NDA 50-718). (b) (4)

This supplement is part of the Applicant's long-term strategy to restore supply of Doxil. The applicant initially proposed (b) (4)

This PAS is also related to IND 36778. The applicant was informed that data from a bioequivalence trial will be necessary to confirm comparability of DP manufactured at a new site (meeting 1/2012), they commenced this trial under the above IND (Amendment dated 3/2013). This trial is underway at the time of this review.

Proposed Changes

PAS S-046 proposes to add a facility, TTY Biopharm, Taiwan, to manufacture DOXIL. No mention of changes to formulation, the process, or methods is made. The following changes are also proposed.

- Change in batch size of DP – from (b) (4) (at BVL/ (b) (4) to (b) (4) at the proposed facility.
- Minor changes in process resulting from changes in equipment at the new site.
- Change in the specification for DP containers and closures – (b) (4) Stoppers.
- Addition of a secondary packaging site: (b) (4)
- Addition of nonclinical data in labeling
- BE study waiver

(b) (4)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 50718/046	Sponsor:	JANSSEN R AND D
Org. Code:	107		920 RT 202 SOUTH
Priority:	3S		RARITAN, NJ 08869
Stamp Date:	12-JUL-2013	Brand Name:	DOXIL
PDUFA Date:	12-NOV-2013	Estab. Name:	
Action Goal:		Generic Name:	DOXORUBICIN HYDROCHLORIDE
District Goal:	08-OCT-2013	Product Number; Dosage Form; Ingredient; Strengths	001; INJECTION, SUSPENSION, LIPOSOMAL; DOXORUBICIN HYDROCHLORIDE; 20MG/10ML 002; INJECTION, SUSPENSION, LIPOSOMAL; DOXORUBICIN HYDROCHLORIDE; 50MG/25ML

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Overall Recommendation:	ACCEPTABLE	on 03-NOV-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 26-JUL-2013	by EES_PROD		

Establishment:	CFN:	FEI:	3005054986
	TTY BIOPHAM CO. LTD 838, SEC. 1 CHUNG-HWA RD. CHUNG-LI, TAOYUAN, TAIWAN, PROVINCE OF CHINA		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE STERILITY TESTER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-NOV-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

(b) (4)

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/s/

KAVITA A VYAS
11/05/2013

HASMUKH B PATEL
11/05/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 050718
Supporting document/s: 139
Applicant's letter date: 12 July 2013
CDER stamp date: 12 July 2013
Product: Doxil
Indication: Ovarian Cancer
Applicant: Janssen Research & Development, LLC
920 Route 202
Raritan, NJ 08869
Review Division: DHOT / DOP2
Reviewer: Shawna L. Weis, PhD
Supervisor/Team Leader: Whitney S. Helms, PhD
Division Director: John K. Leighton, PhD, DABT (DHOT) / Patricia Keegan, MD (DOP2)
Project Manager: Anuja Patel, MPH

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 050718 are owned by Janssen Research and Development, LLC or are data for which [name of applicant] has obtained a written right of reference. Any information or data necessary for approval of NDA 050718 that Janssen Research and Development, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 050718.

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1 Executive Summary

1.1 Introduction

In 2012 Due to compliance problems at their Bedford, Ohio manufacturing site (Bon Venue Laboratories; BVL), Janssen undertook the process of qualifying a replacement manufacturing site(s) for DOXIL to assure long-term supply of the drug to the US market.

In March 2012, Janssen started qualification activities at Taiwan-based TTY Biopharm (TTY) as a replacement manufacturing site for DOXIL. Due to the limited supply of available drug, and the time required to recruit patients with ovarian cancer (the labeled indication), the Sponsor would like to submit animal data to meet the bioequivalence requirement to allow drug product manufactured at the new TTY site to enter the US market.

The purpose of this submission is, therefore, to provide nonclinical bioequivalence data for two lots of Doxil drug product manufactured by Janssen at different sites, the reference lot, manufactured at BVL, and the comparator lot, manufactured at TTY.

To support its bioequivalence waiver, the Sponsor conducted nonclinical studies to establish the extent of similarity between the BVL and TTY products. In these studies, the Sponsor evaluated material from the two sources for overall pharmacokinetic similarity, as well as similarity of tissue distribution, and efficacy in a tumor model.

On the basis of plasma exposures, the two sources of material achieved bioequivalence when administered by IV bolus injection to rats (1 mg/kg) and mice (6 mg/kg); however, they were not bioequivalent for tissue distribution kinetics. As tissue distribution is not typically assessed for the purposes of bioequivalence testing, the relevance of this observation to the question of bioequivalence is unclear.

There was also no effect of manufacturing location on the biological activity in mouse breast adenocarcinoma xenografts, as there were no differences between the BVL and TTY products in (1) overall plasma exposure, (2) tissue distribution to tumors, or (3) tumor growth suppression, between the two treatment arms at the doses evaluated.

The weight of evidence suggests that the two lots of material are bioequivalent in animals for the primary endpoint of overall plasma exposure, and for apparent distribution to tumors. The two lots differ with regard to biodistribution to normal organs; however, as this is not a parameter that is typically evaluated in bioequivalence studies, it is unclear what that observation signifies.

1.3 Recommendations

1.3.1 Approvability

Not approvable. Per FDA's teleconference with Janssen on 23 July 2013, animal bioequivalence data cannot substitute for human bioequivalence data in support of a change in manufacturing site for a drug product marketed in the United States.

1.3.2 Additional Non Clinical Recommendations

2 Drug Information

2.1 Drug

CAS Registry Number

(b) (4)

Generic Name

doxorubicin hydrochloride liposome injection

Code Name

N/A

Chemical Name

Doxorubicin: (b) (4)

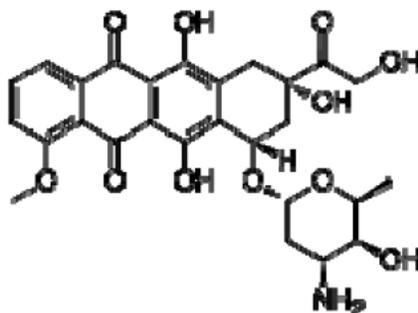
Liposome: N-(Carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-snglycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)

Molecular Formula/Molecular Weight

Doxorubicin: $C_{27}H_{29}NO_{11}$ / (b) (4)

Structure or Biochemical Description

Doxorubicin Structure:



Pharmacologic Class

Anthracycline topoisomerase inhibitor

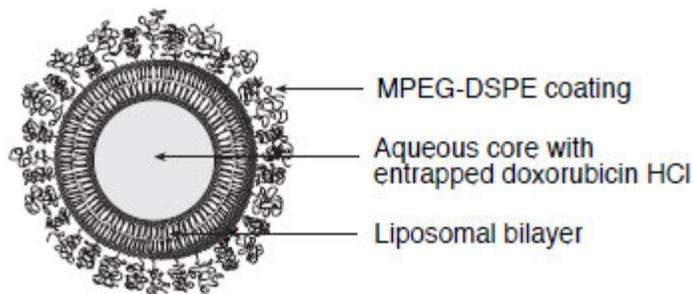
2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 50718

2.3 Drug Formulation

Doxil is doxorubicin HCl liposomes composed of surface-bound methoxypolyethylene glycol (MPEG), surrounding a phospholipid bilayer (Sponsor-Figure 1, from the Doxil Product Label)

Figure 1: Doxil Liposome Structure



2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None known

3 Studies Submitted

3.1 Studies Reviewed

- ❖ Investigation of the anti-tumor efficacy of two Caelyx® formulations in the MDA-MB-231 breast cancer model in female NMRI Nude (Nu/Nu) mice (JNJ-17302753-AAC)
- ❖ Pharmacokinetics of JNJ-17302753-AAC in female NMRI Nude (Nu/Nu) mice after single intravenous administration of Caelyx/Doxil reference and test formulations at 6 mg/kg.
- ❖ Pharmacokinetics and tissue distribution of doxorubicin (JNJ-17302753) in male Sprague-Dawley rats after single intravenous dose administration of doxorubicin HCl liposome injection Doxil/Caelyx® at 1 mg/kg
- ❖ Pharmacokinetics and tissue distribution of doxorubicin (JNJ-17302753) in the male mouse after single intravenous dose administration of doxorubicin HCl liposome injection Doxil/Caelyx® at 6 mg/kg
- ❖ Pharmacokinetics of doxorubicin in the Sprague Dawley rat after single intravenous dose administration of doxorubicin HCl liposome injection (JNJ-17302753-AAC) at 1 mg/kg
- ❖ JNJ-17302753-AAC: Pharmacokinetics and Tissue Distribution of Doxorubicin in

the Male Sprague-Dawley Rat after Single Intravenous Bolus Dose Administration of Doxorubicin HCl Liposome Injection at 1 mg/kg

- ❖ JNJ-17302753-AAC: Pharmacokinetics and Tissue Distribution of Doxorubicin in the Male Mouse after Single Intravenous Bolus Dose Administration of Doxorubicin HCl Liposome Injection at 6 mg/kg

Method Validation



3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

4 Pharmacology

4.1 Primary Pharmacology

Study title: Investigation of the anti-tumor efficacy of two Caelyx® formulations in the MDA-MB-231 breast cancer model in female NMRI Nude (Nu/Nu) mice

Study no.: OIV.12.4243

Study report location: 4.2.1.1

Conducting laboratory and location: Janssen Research & Development

Division of Janssen Pharmaceutica N.V.

Turnhoutseweg 30

B-2340 Beerse (Belgium)

Date of study initiation: 28 December 2012

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Lot numbers were not supplied for either test article.

This study compares the pharmacokinetic exposures of TTY Doxil to BVL Doxil in MDA-MB-231-breast adenocarcinoma-bearing NMRI nude mice. The study was not conducted in accordance with Good Laboratory Practices.

A summary of the study outcome is provided in Table 1 and Sponsor-Figure 2. Both pairs of treatment regimens exhibited similar anti-tumor responses, as demonstrated in Sponsor-Figure 2. Only the vehicle-treatment groups exhibited differences in the rate of tumor growth (*). In addition, whereas all treatment arms were statistically different from the corresponding vehicle arm (i.e., anti-tumor activity was demonstrated), neither treatment group was statistically different from its comparator at any timepoint.

At the end of study, when tumors were excised and weighed, there were no differences between the BVL or TTY formulations in the measured tumor weights, though all were statistically different from their respective vehicle controls (Sponsor-Figure 3).

Table 1: Summary of Tumor Volume Results

Regimen	Initial Body Weight	Final Body Weight	Initial Tumor Vol	Final Tumor Vol.
BVL Vehicle	28.19±0.66	30.66±0.76	151.14±9.78	537.23±43.47
TTY Vehicle	29.05±0.42	31.27±0.32	150.87±12.29	490.08±44.19
BVL 3 mg/kg	28.32±0.55	30.98±0.62	152.97±12.71	252.51±23.78
BVL 6 mg/kg	28.61±0.36	29.46±0.46	144.19±10.02	133.88±8.19
TTY 3 mg/kg	29.98±0.62	26.98±0.26	150.59±7.61	244.60±20.53
TTY 6 mg/kg	27.73±0.26	29.86±0.45	144.37±15.59	137.59±12.74

N = 12F/Group
 0.1 mL of 5X10⁷ cell/mL suspended in matrigel and DMEM (1:1) was injected into the mammary fat pad.
 Doses were given QW X 4

Figure 2: Effect of Doxil Exposure on Tumor Growth in NDA-MB-231 Nu/Nu Xenografts

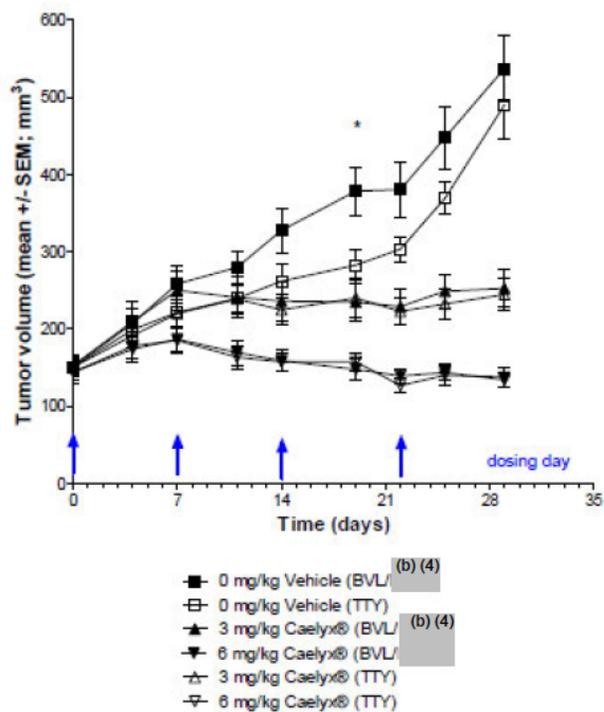
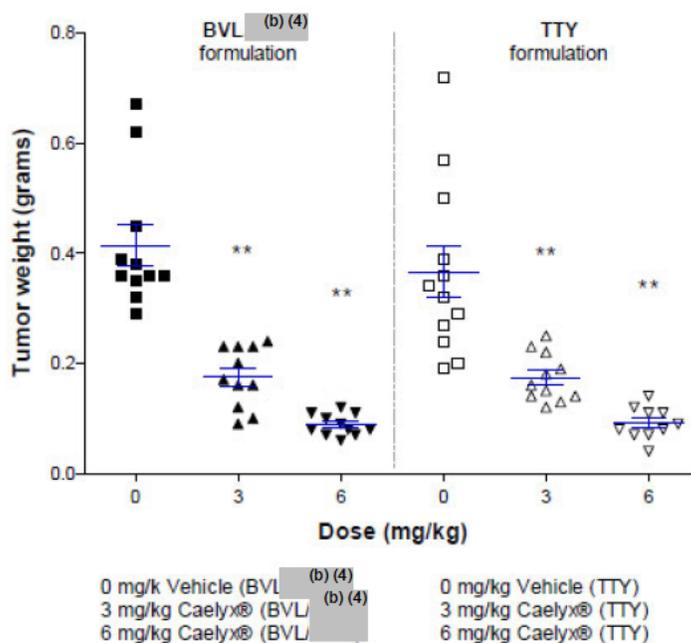


Figure 3: Summary of Terminal Tumor Weights vs. Supplier and Regimen

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Title: Pharmacokinetics of JNJ-17302753-AAC in female NMRI Nude (Nu/Nu) mice after single intravenous administration of Caelyx/Doxil reference and test formulations at 6 mg/kg.

Study no.: FK10435

Study report location: 4.2.1.1

Conducting laboratory and location: Janssen Research & Development

Division of Janssen Pharmaceutica N.V.

Turnhoutseweg 30

B-2340 Beerse (Belgium)

Date of study initiation: Not provided

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Lot numbers were not supplied for either test article.

Methods

Doses: 0, 3, 6 mg/kg
Frequency of dosing: QWk X 4
Route of administration: IV
Dose volume: 10 mL/kg
Formulation/Vehicle:
Species/Strain: Mouse, NMRI nude (Nu/Nu)
Number/Sex/Group: 42 females (6/timepoint)
Age: Not specified
Weight: 30 g at the start of the study
Satellite groups: None
Unique study design: Tumor-bearing

The purpose of this study was to evaluate the pharmacokinetics of IV doxil administered to nu/nu mice at a dose of 6 mg/kg, with the intent of supporting the tumor growth inhibition study (OIV.12.4243). Animals were tumor-bearing. Tumors were implanted on 22 January 2013.

As illustrated in Sponsor-Table 1 and Sponsor-Figure 4, doxorubicin plasma exposures were considered similar between the two sources of drug (BVL and TTY), as the mean AUC_{∞} and AUC_{0-120h} values were within 7% of one another, and mean tumor exposures were within 3% of one another.

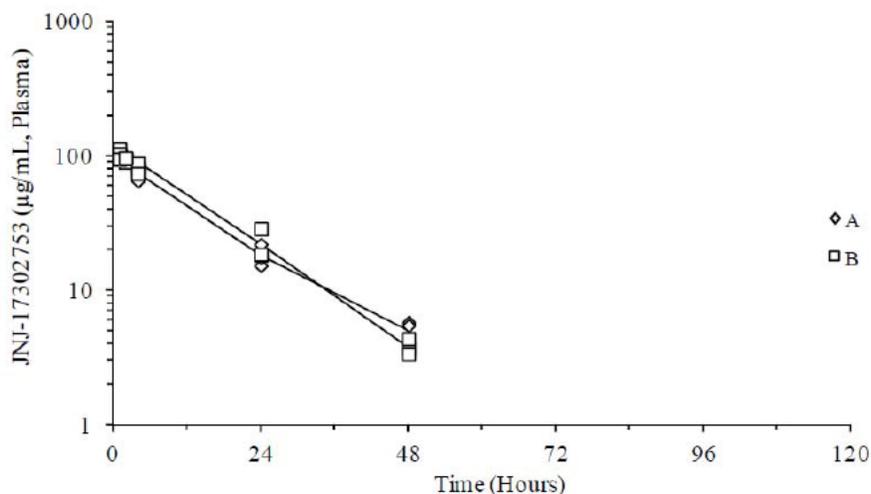
Of note, the terminal half-life estimate was shorter for the TTY material, for reasons that aren't immediately apparent, as the clearance was highly similar between the BVL and TTY sources of material. The proportion of the AUC that was extrapolated for the purposes of estimating the terminal elimination half-life was higher in the BVL AUC_{∞} than for the TTY AUC_{∞} estimate; thus, it is possible that the extrapolation affected the calculation of half-life.

Table 2: Pharmacokinetic Summary of Doxil Exposure in Tumor-Bearing nu/nu Mice from the BVL and TTY Manufacturing Sites

	A: BVL ^{(b) (4)} (Reference)		B: TTY (Test)	
	Plasma	Tumor	Plasma	Tumor
C _{max} (µg/mL)	104	1.63	104	1.86
T _{max} (h)	1	48	1	24
AUC _{0-t} ¹ (µg.h/mL)	1438	149	1542	144
AUC _{0-inf} (µg.h/mL)	1532	256	1595	255
% AUCextrapolated	6.1	33	3.3	46
Cl (L/h/kg)	0.0039	NA ²	0.0038	NA ²
Vd (L/kg)	0.073	NA ²	0.052	NA ²
t _{1/2} ³ (h)	13	67	9.5	98

¹ 48 h for plasma, 120 h for tumor; ² NA: Not Applicable; ³ plasma: t_{1/2, 24-48h}, tumor: t_{1/2, 48-120h}

Figure 4: Individual Concentration Time Profiles in nu/nu Mice Following a Single IV Injection of Doxil from BVL and TTY Manufacturing Sites



Study title: Pharmacokinetics and tissue distribution of doxorubicin (JNJ-17302753) in male Sprague-Dawley rats after single intravenous dose administration of doxorubicin HCl liposome injection Doxil/Caelyx® at 1 mg/kg

Study no.: TOX10377

Study report location: 4.2.2.2

Conducting laboratory and location: (b) (4), Beerse site

Turnhoutseweg 30

B-2340 Beerse, Belgium

Date of study initiation: Not stated

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Not stated

Methods

Doses: 1 mg/kg

Frequency of dosing: Single dose

Route of administration: IV

Dose volume: 2.5 mL/kg

Formulation/Vehicle: Composition not provided

Species/Strain: Rat, Sprague Dawley

Number/Sex/Group: 5M/timepoint

Age: Not specified

Weight: Not specified

Satellite groups: None

Unique study design: Tissue Distribution

Deviation from study protocol: Unknown

The stated purpose of this study was to evaluate the pharmacokinetics and tissue distribution of doxorubicin in the SD rat following receipt of a single IV dose of 1 mg/kg (2.5 mL/kg) of a clinical formulation of Doxil. A secondary objective was to determine if the Sponsor could demonstrate bioequivalence (AUC, C_0 (total doxorubicin) and/or C_{max}) for free doxorubicin and C_{max} for total doxorubicin in tissues, when the same formulation of test article is given to two groups of rats.

Plasma samples were collected at 0.083, 0.5, 1, 4, 8, 24, 48, 96, and 120 hours post-dose. 5 animals were sampled per timepoint.

As illustrated in Sponsor-Figure 5 and Sponsor-Figure 6, significant discrepancies exist between Group A and Group B plasma concentration-time profiles for both free and total doxorubicin concentrations.

Figure 5: Mean plasma concentration-time profiles of total doxorubicin in male rats following a single IV dose of 1 mg/kg Doxil

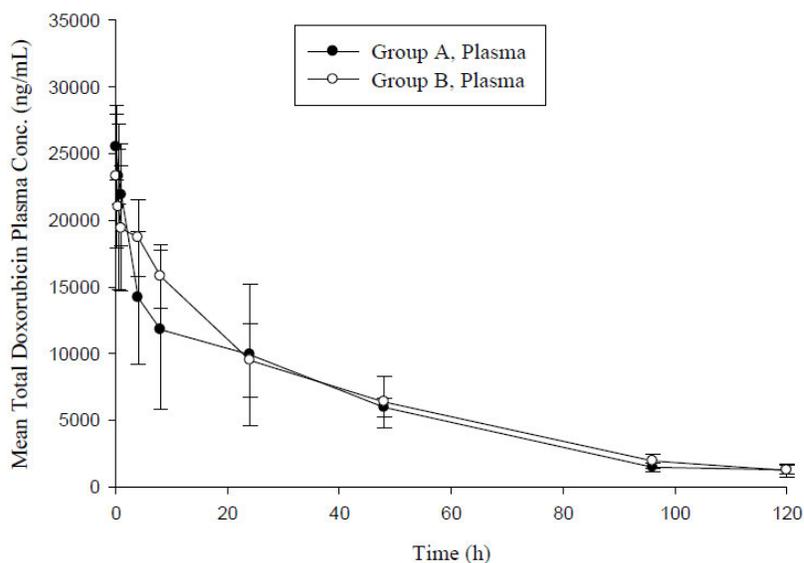
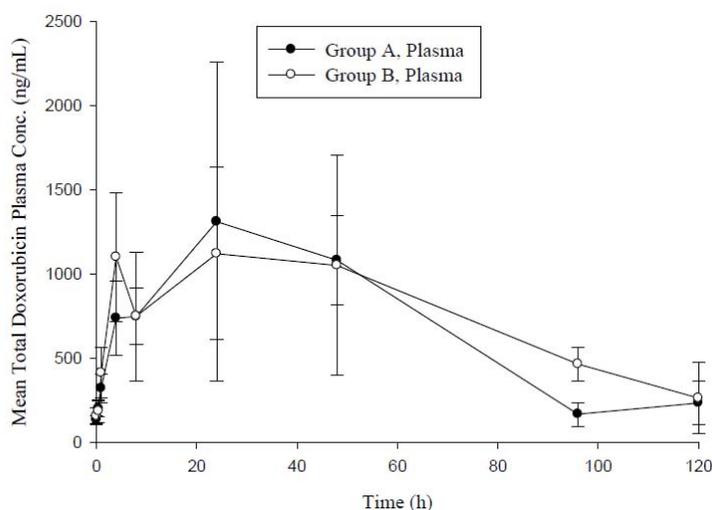


Figure 6: Mean plasma concentration-time profiles of free doxorubicin in male rats following a single IV injection of 1 mg/kg Doxil



Discrepant tissue distributions were also observed, as illustrated in Sponsor-Figure 7 and Sponsor-Figure 8. As demonstrated in Sponsor-Table 4, Except for $AUC_{0-\infty}$ in the heart and liver, the data from plasma and tissue-distribution samples failed to demonstrate that A and B were bioequivalent, by the standard 90% confidence limits (0.80-1.25).

Figure 7: Mean concentrations of doxorubicin in heart, kidney and spleen following a single IV injection in male rats

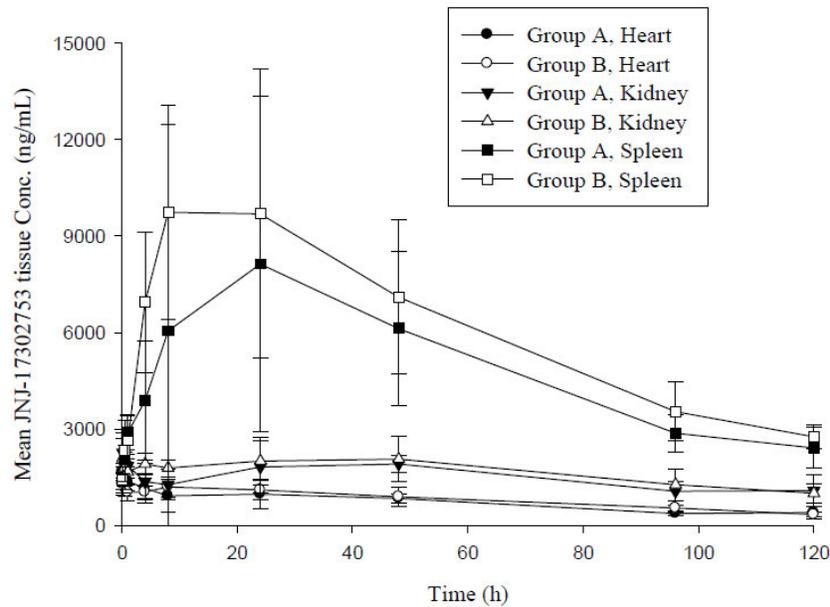


Figure 8: Mean concentrations of doxorubicin in lung and liver following a single IV injection in male rats

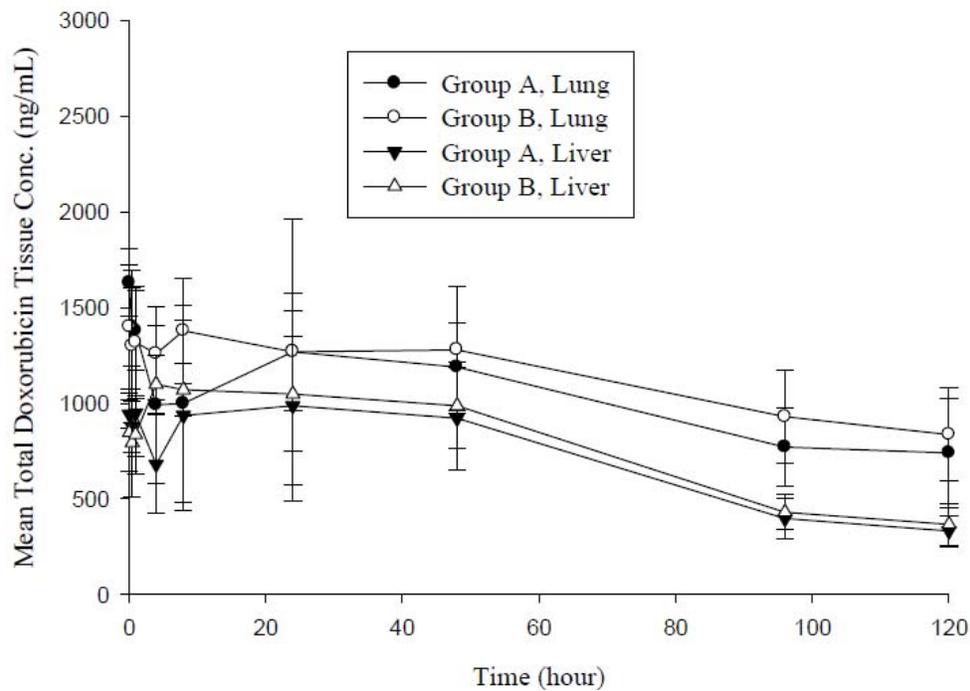


Table 3: Pharmacokinetic parameters for total and free doxorubicin in heart, kidney, lung, liver and spleen following a single IV injection of 1 mg/kg Doxil in the male SD rat

Analyte	Tissue	Group	C ₀ (ng/mL)	C _{max} ^b (ng/mL)	AUC _{0-∞} (ng•h/mL)	AUC _{0-120h} (ng•h/mL)	t _{1/2} (h)
Total Doxorubicin	Heart	A		1670	120000 ^a	83100	63.6
Total Doxorubicin	Heart	B		1300	121000	94900	53.1
Total Doxorubicin	Kidney	A		2270	303000 ^a	176000	81.2
Total Doxorubicin	Kidney	B		2080	298000 ^a	199000	68.9
Total Doxorubicin	Spleen	A		8130	765000	584000	51.9
Total Doxorubicin	Spleen	B		9740	933000	726000	52.0
Total Doxorubicin	Lung	A		1630	228000 ^a	121000	100
Total Doxorubicin	Lung	B		1400	275000 ^a	136000	115
Total Doxorubicin	Liver	A		987	106000	83500	47.4
Total Doxorubicin	Liver	B		1100	117000	91300	48.6
Total Doxorubicin	Plasma	A	26000		734000	677000	31.0
Total Doxorubicin	Plasma	B	23800		805000	751000	30.2
Free Doxorubicin	Plasma	A		1310	87800	78000	29.1
Free Doxorubicin	Plasma	B		1120	104000	90000	36.6

^a: AUC% extrapolated greater than 25% of the total AUC, reported but excluded from discussion

^b: observed value

Table 4: Rat bioequivalence summary from study TOX10377

Parameter	Tissue	Ratio	90% Conf Interval	Test
C ₀	Plasma Total	0.91	(0.68, 1.23)	Partial
C _{max}	Plasma Free	0.86	(0.31, 2.36)	Not Bioequivalent
AUC _{0-∞}	Plasma Total	1.11	(0.95, 1.28)	Not Bioequivalent
AUC _{0-∞}	Plasma Free	1.12	(0.86, 1.47)	Not Bioequivalent
AUC _{0-120h}	Plasma Total	1.10	(0.93, 1.31)	Not Bioequivalent
AUC _{0-120h}	Plasma Free	1.09	(0.80, 1.49)	Not Bioequivalent

Parameter	Tissue	Ratio	90% Conf Interval	Test
C_{max}	Heart	0.78	(0.52, 1.17)	Not Bioequivalent
C_{max}	Kidney	0.92	(0.58, 1.47)	Not Bioequivalent
C_{max}	Liver	1.11	(0.60, 2.06)	Not Bioequivalent
C_{max}	Lung	0.80	(0.54, 1.17)	Not Bioequivalent
C_{max}	Spleen	1.20	(0.51, 2.81)	Not Bioequivalent

Parameter	Tissue	Ratio	90% Conf Interval	Test
$AUC_{0-\infty}$	Heart	1.01	(0.85, 1.20)	** Bioequivalent
$AUC_{0-\infty}$	Kidney	0.98	(0.79, 1.22)	Not Bioequivalent
$AUC_{0-\infty}$	Spleen	1.23	(0.97, 1.57)	Not Bioequivalent
$AUC_{0-\infty}$	Lung	1.20	(0.96, 1.51)	Not Bioequivalent
$AUC_{0-\infty}$	Liver	1.04	(0.94, 1.14)	** Bioequivalent
AUC_{0-120h}	Heart	1.14	(0.97, 1.33)	Not Bioequivalent
AUC_{0-120h}	Kidney	1.12	(0.95, 1.33)	Not Bioequivalent
AUC_{0-120h}	Spleen	1.24	(0.97, 1.58)	Not Bioequivalent
AUC_{0-120h}	Lung	1.12	(0.96, 1.31)	Not Bioequivalent
AUC_{0-120h}	Liver	1.09	(0.92, 1.29)	Not Bioequivalent

Study title: Pharmacokinetics and tissue distribution of doxorubicin (JNJ-17302753) in the male mouse after single intravenous dose administration of doxorubicin HCl liposome injection Doxil/Caelyx[®] at 6 mg/kg

Study no.: TOX10439

Study report location: 4.2.2.2

Conducting laboratory and location: (b) (4), Beerse site

Turnhoutseweg 30

B-2340 Beerse, Belgium

Date of study initiation: Not stated

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Not stated

Methods

Doses: 6 mg/kg
Frequency of dosing: Single dose
Route of administration: IV
Dose volume: 10 mL/kg
Formulation/Vehicle: Clinical formulation diluted in 5.5% dextrose
Species/Strain: Mouse, SPF albino Swiss
Number/Sex/Group: 5-6M/timepoint
Age: Not specified
Weight: Based on terminal body weights, 27.1-35.3 g
Satellite groups: None
Unique study design: Tissue Distribution
Deviation from study protocol: Unknown

The stated purpose of this study was to evaluate the pharmacokinetics and tissue distribution of doxorubicin in the male SPF Swiss white mouse following receipt of a single IV dose of 6 mg/kg (10 mL/kg) of a clinical formulation of Doxil. A secondary objective was to determine if the same formulation would meet the requirements of bioequivalence for AUC and C_0 (total doxorubicin) or C_{max} for free doxorubicin and C_{max} for total doxorubicin in tissues.

A secondary objective was to determine if parallel comparisons of the same formulation could meet the requirements of bioequivalence when administered to two groups of mice.

Plasma samples were collected at 0.083, 0.5, 1, 4, 8, 24, 48, 96, and 120 hours post-dose. 5 animals were sampled per timepoint.

The results of the study indicated that the plasma concentrations achieved in Groups A and B met the criteria for bioequivalence (0.80-1.25) for AUC_{0-120h} and AUC_{∞} for all tissues but the spleen, where it missed the cutoff by 1% for AUC_{0-120h} .

Figure 9: Mean plasma concentration-time profiles of total doxorubicin in male mice following a single IV dose of 6 mg/kg Doxil®

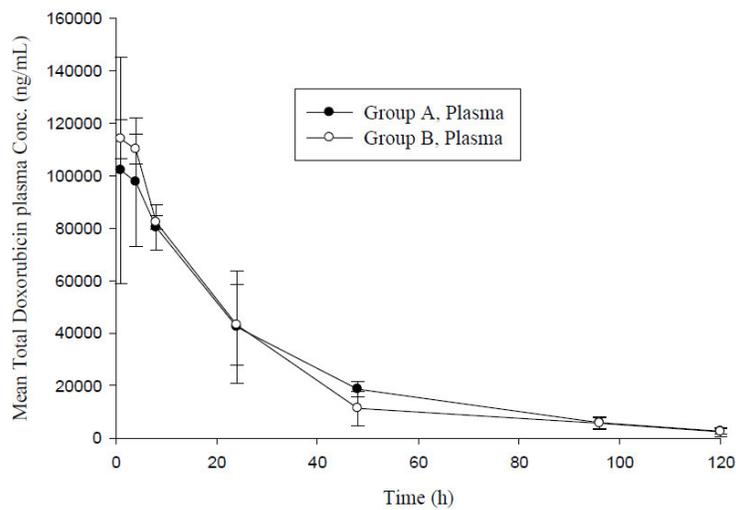


Figure 10: Mean concentrations of doxorubicin in heart, kidney and spleen following a single IV injection of 6 mg/kg Doxil® in male mice

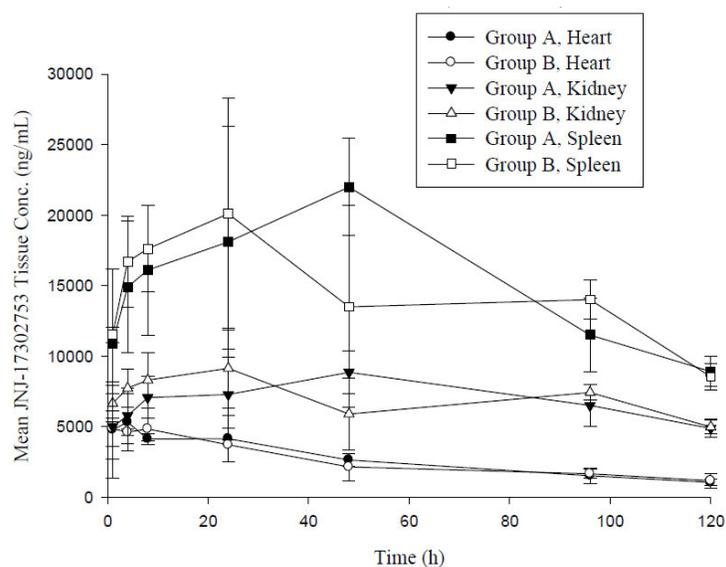
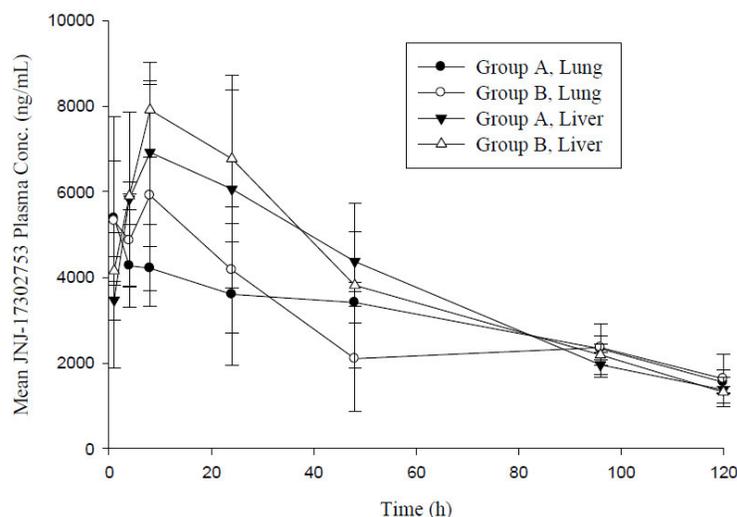


Figure 11: Mean concentrations of doxorubicin in lung and liver following a single IV injection of 6 mg/kg Doxil® in male mice



Based upon the data in Sponsor-Table 5, the Sponsor concludes that the data meet the cutoff for bioequivalence; however, it should be noted, that using the pharmacokinetic parameters for total doxorubicin that are provided in the PK report, there are discrepancies with the exposure ratios (AUC_{∞}) obtained and those given in Sponsor-Table 5. Compare the values in Sponsor-Table 5 with Reviewer-Table 6, the exposures for which are derived from Sponsor PK-Table 7. It is unclear how these discrepancies would have changed the interpretation of bioequivalence, as the confidence intervals would need to be recalculated.

Table 5: Summary of organ and plasma exposures

Parameter	Tissue	Ratio ^a	90% Conf Interval	Bioequivalence (0.80 – 1.25)
$AUC_{0-\infty}$	Plasma Total	0.94	(0.82, 1.09)	Meets the criteria
$AUC_{0-\infty}$	Heart	1.04	(0.90, 1.21)	Meets the criteria
$AUC_{0-\infty}$	Kidney	1.01	(0.92, 1.10)	Meets the criteria
$AUC_{0-\infty}$	Liver	1.01	(0.89, 1.15)	Meets the criteria
$AUC_{0-\infty}$	Lung	1.07	(0.92, 1.24)	Meets the criteria
$AUC_{0-\infty}$	Spleen	1.07	(0.97, 1.18)	Meets the criteria
AUC_{0-120h}	Plasma Total	0.94	(0.81, 1.09)	Meets the criteria
AUC_{0-120h}	Heart	0.95	(0.83, 1.10)	Meets the criteria
AUC_{0-120h}	Kidney	0.98	(0.87, 1.12)	Meets the criteria
AUC_{0-120h}	Liver	1.03	(0.88, 1.19)	Meets the criteria
AUC_{0-120h}	Lung	0.96	(0.83, 1.11)	Meets the criteria
AUC_{0-120h}	Spleen	0.92	(0.79, 1.07)	Not met the criteria*

^a ratio of mean group B value to mean group A value.

* as the lower limit of the 90% confidence interval was only minimally below the criterium (0.80), bioequivalence was considered achieved.

Table 6: Exposure Ratios for Tested Organs in the Mice (Reviewer Table)

	AUC_∞	AUC_{0-120h}
Heart, Ratio B:A	394000	312000
	443000	299000
	1.1244	0.9583
Kidney, Ratio B:A	1460000	856000
	2060000	844000
	1.411	0.986
Liver, Ratio B:A	539000	454000
	562000	469000
	1.0427	1.033
Lung, Ratio B:A	513000	365000
	571000	349000
	1.113	0.9562
Spleen, Ratio B:A	2590000	1890000
	3350000	1750000
	1.2934	0.9259

Table 7: Summary of Pharmacokinetic Parameters (N=6) for Total Doxorubicin in Male Mice Following a 6 mg/kg IV Injection of Doxil

Analyte	Tissue	Group	C ₀ (ng/mL)	C _{max} ^b (ng/mL)	t _{max} ^b (h)	AUC _{0-∞} (ng•h/mL)	AUC _{0-120h} (ng•h/mL)	t _{1/2} (h)
Total Doxorubicin	Heart	A		5320	4.00	394000	312000	54.4
Total Doxorubicin	Heart	B		4860	1.00	443000 ^a	299000	86.1
Total Doxorubicin	Kidney	A		8860	48	1460000 ^a	856000	86.4
Total Doxorubicin	Kidney	B		9140	24	2060000 ^a	844000	169
Total Doxorubicin	Spleen	A		22000	48	2590000 ^a	1890000	54.6
Total Doxorubicin	Spleen	B		20100	24	3350000 ^a	1750000	130
Total Doxorubicin	Lung	A		5380	1.00	513000 ^a	365000	65.9
Total Doxorubicin	Lung	B		5910	8.00	571000 ^a	349000	94.4
Total Doxorubicin	Liver	A		6920	8.00	539000	454000	42.8
Total Doxorubicin	Liver	B		7910	8.00	562000	469000	48.6
Total Doxorubicin	Plasma	A	104000			3120000	3020000	25.8
Total Doxorubicin	Plasma	B	115000			2970000	2850000	33.7

^a: AUC% extrapolated greater than 25% of the total AUC, reported but excluded from discussion.

^b: observed value

Study title: Pharmacokinetics of doxorubicin in the Sprague Dawley rat after single intravenous dose administration of doxorubicin HCl liposome injection (JNJ-17302753-AAC) at 1 mg/kg

Study no.: TOX10462
Study report location: 4.2.2.2
Conducting laboratory and location: (b) (4) Beerse site
Turnhoutseweg 30
B-2340 Beerse, Belgium
Date of study initiation: Not stated
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Not stated

Methods

Doses: 1 mg/kg
Frequency of dosing: Single dose
Route of administration: IV
Dose volume: 2.5 mL/kg
Formulation/Vehicle: Clinical formulation diluted in 5.5% dextrose
Species/Strain: Rat, Sprague Dawley
Number/Sex/Group: 6M/timepoint
Age: Not specified
Weight: Not specified
Satellite groups: None
Unique study design:
Deviation from study protocol: Unknown

The purpose of this study was to determine whether IV infusion of a single formulation of Doxil[®] to two groups of rats would produce bioequivalent results. A month later, second group of 12 rats/timepoint (6/group/timepoint; 2 groups) was evaluated for bioequivalence when Doxil[®] was administered by IV bolus injection.

As indicated by the 90% confidence intervals given in Table 9, administration of a 6 mg/kg dose of Doxil[®] by IV infusion did not result in exposures that met the criteria for bioequivalence, however, when Doxil[®] was administered by the IV bolus route, they did.

The concentration-time profiles for these two experiments (Table 9) demonstrate a high degree of overlap in the concentration profiles, as illustrated in Sponsor-Figure 12 and Sponsor-Figure 13 for replicate 1 and replicate 2, respectively. The Sponsor's interpretation of the bioequivalence of these two groups is provided in Sponsor-Table 8. Note that because the upper bound of the 90% confidence interval exceeded the criteria for bioequivalence, the results obtained when the formulation was administered by the infusion route, were not considered bioequivalent.

Table 8: Bioequivalence summary for infused vs. bolus-injected Doxil® at a dose of 1 mg/kg in the rat

Dosing method (groups)	Parameter	Tissue	Ratio ^a	90% Conf Interval	Bioequivalence (0.80 – 1.25)
Infusion (B/A)	C ₀	Plasma Total	1.18	(0.90, 1.55)	Criteria not met
	AUC _{0-∞}	Plasma Total	1.11	(0.92, 1.33)	Criteria not met
	AUC _{0-120h}	Plasma Total	1.11	(0.93, 1.33)	Criteria not met
Bolus (E/D)	C ₀	Plasma Total	0.99	(0.94, 1.04)	Meets the criteria
	AUC _{0-∞}	Plasma Total	1.03	(0.95, 1.12)	Meets the criteria
	AUC _{0-120h}	Plasma Total	1.04	(0.96, 1.12)	Meets the criteria

^a ratio of mean group B value to mean group A value (infusion) or ratio of mean group E value to mean group D value (bolus)

Table 9: Summary of PK results and BE conclusions for mean total doxorubicin levels following administration of 1 mg/kg Doxil® by IV infusion or bolus injection

Route, Group	C ₀ (ng/mL)	AUC _∞ (ng*hr/mL)	AUC _{0-120h} (ng*hr/mL)	T _{1/2} (hr)
Infusion, Group A	21000 ±6740	760000±175000	716000±159000	28.5±4.47
Infusion, Group B	23400±3670	848000±109000	800000±101000	59.4±2.64
Infusion B:A	1.11	1.11	1.11	--
90% CI	(0.90, 1.55)	(0.92, 1.33)	(0.93, 1.33)	--
<i>Conclusion</i>	<i>Not met</i>	<i>Not met</i>	<i>Not met</i>	--
IV Bolus A	26600±1300	802000±72800	759000±56800	29.64
IV Bolus B	25800±1770	826000±66500	786000±58100	27.4±3.94
Bolus B:A	0.97	1.03	1.04	--
90% CI	(0.94, 1.04)	(0.95, 1.12)	(0.96, 1.12)	--
<i>Conclusion</i>	<i>Met</i>	<i>Met</i>	<i>Met</i>	

Yellow highlight denotes discordant value relative to Table 8

Figure 12: Replicate 1, mean plasma concentrations of total doxorubicin in male rats (N = 6) following a single IV infusion and a single IV bolus dose of 1 mg/kg Doxil®

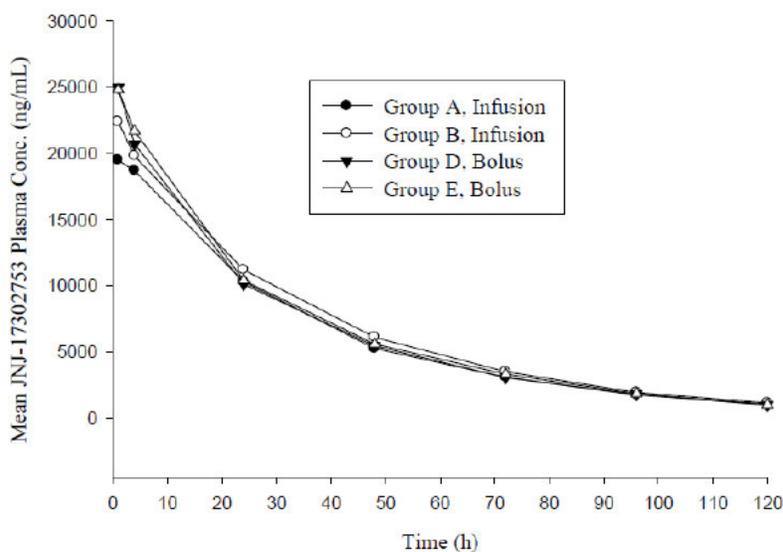
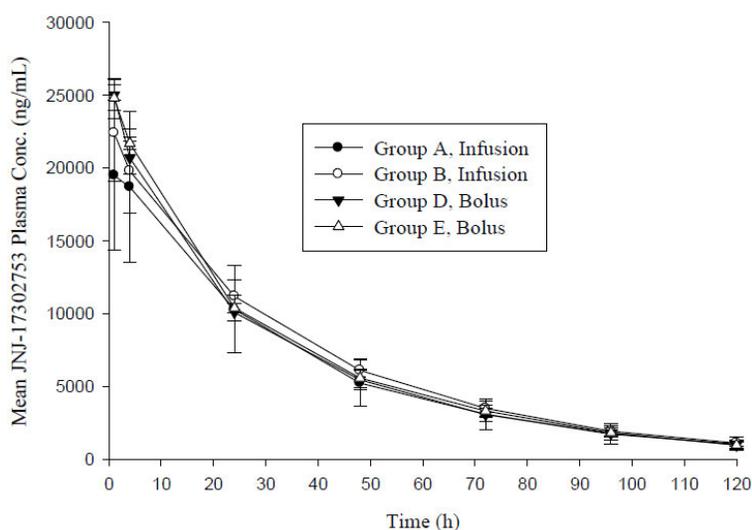


Figure 13: Replicate 2, mean plasma concentrations of total doxorubicin in male rats (N = 6) following a single IV infusion and a single IV bolus dose of 1 mg/kg Doxil®



Study title: JNJ-17302753-AAC: Pharmacokinetics and Tissue Distribution of Doxorubicin in the Male Sprague-Dawley Rat after Single Intravenous Bolus Dose Administration of Doxorubicin HCl Liposome Injection at 1 mg/kg

Study no.: TOX10506

Study report location: 4.2.2.2

Conducting laboratory and location: (b) (4) Beerse site

Turnhoutseweg 30

B-2340 Beerse, Belgium

Date of study initiation: Not stated

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: Group A: BVL Batch 1207168

Group B: TTY Batch DCXIA1201

Methods

Doses: 1 mg/kg
Frequency of dosing: Single dose
Route of administration: IV
Dose volume: 2.5 mL/kg
Formulation/Vehicle: Clinical formulation diluted in 5.5% dextrose
Species/Strain: Rat, Sprague Dawley
Number/Sex/Group: 6M/timepoint
Age: Not specified; ordered by body weight
Weight: 259-304 grams on first day of dosing
Satellite groups: None
Unique study design: Tissue distribution
Deviation from study protocol: Unknown

The purpose of this study was to compare the PK and tissue distribution of Doxil produced by two different manufacturing sites for the purposes of supporting Janssen's bioequivalency waiver. Janssen intended to use animal data to support their claim of similarity between the two sites rather than completing a human bioequivalence study.

Two arms were used in this study. Group A material was manufactured at Ben Venue Laboratories, Inc., Bedford OH, and Group B material was manufactured at TTY Biopharmaceuticals, in Taiwan. There were 6 rats/timepoint (7 timepoints) for each treatment arm. At each timepoint, 6 male rats per treatment arm were euthanized for plasma and tissue collection. For both treatment arms, a single IV bolus dose of 1 mg/kg was administered via the tail vein.

The plasma and tissue pharmacokinetic parameters are provided in Sponsor-Table 10.

Table 10: Summary of pharmacokinetic plasma and tissue exposures for BVL- and TTY-treated rats

Group	Manufacturer	Tissue/ Plasma	C ₀ (ng/mL)	C _{max} ^a (ng•h/mL or g)	t _{max} ^a (h)	AUC _{0-∞} (ng•h/mL or g)	AUC _{0-144h} (ng•h/mL or g)	t _{1/2} (h)
A (Reference)	Ben Venue Laboratories Inc. (United States)	(b) (4) Plasma	25200			850000	822000	30.5
B	TTY Biopharm Company Ltd. (Taiwan)	Plasma	25400			882000	828000	35.6
A (Reference)	Ben Venue Laboratories Inc. (United States)	(b) (4) Heart		718	4.00	75700	67500	44.1
B	TTY Biopharm Company Ltd. (Taiwan)	Heart		728	4.00	67700	53400	62.7
A (Reference)	Ben Venue Laboratories Inc. (United States)	(b) (4) Kidney		1560	24	321000 ^b	186000	113
B	TTY Biopharm Company Ltd. (Taiwan)	Kidney		1510	48	273000 ^b	169000	96.5
A (Reference)	Ben Venue Laboratories Inc. (United States)	(b) (4) Spleen		10200	24	1320000 ^b	885000	80.8
B	TTY Biopharm Company Ltd. (Taiwan)	Spleen		10500	24	1470000 ^b	990000	80.6
A (Reference)	Ben Venue Laboratories Inc. (United States)	(b) (4) Lung		1140	24	125000	103000	55.7
B	TTY Biopharm Company Ltd. (Taiwan)	Lung		1300	48	201000 ^b	129000	84.8
A (Reference)	Ben Venue Laboratories Inc. (United States)	(b) (4) Liver		1340	24	142000	113000	62.6
B	TTY Biopharm Company Ltd. (Taiwan)	Liver		1270	4.00	145000	113000	61.8

^a: observed value (tissue t_{max} is an approximation of observed values, there were no intermediate samples collected between 4 and 24 h or 24 and 48 h)

^b: AUC% extrapolated greater than 25% of the total AUC

*: data derived from N = 6 per timepoint with samples collected over 1 to 144 h post-dose (sparse study design)

As illustrated in Sponsor-Figure 15 and Sponsor-Table 11, plasma concentrations achieved with these two lots of material were considered bioequivalent (within the range of the 90% confidence limits (0.80-1.25) of the reference article).

Sponsor-Figure 14-Figure 20. provide a graphical illustration of the range of measured concentrations observed in each tissue type at each timepoint, as well as a comparison of the measured concentrations for the two material sources. There was considerable variation in concentration over the duration of sampling, which likely represents the distribution phase for the respective tissue; however, there was also a substantial

temporal variation in achieved tissue concentrations between the two sources of material, particularly for the spleen and lung.

Indeed, not all tissues met the criteria for bioequivalence, as indicated in Sponsor-Table 12. In particular, the upper confidence intervals for the lung and spleen, and the lower confidence interval for the heart, failed to demonstrate bioequivalence. The concentration-time profiles for the individual tissues are graphically depicted in Sponsor-Figure 14-Figure 20.

Figure 14: Kinetics of tissue distribution in the rat using two sources of Doxil® [BVL (A) and TTY (B)]

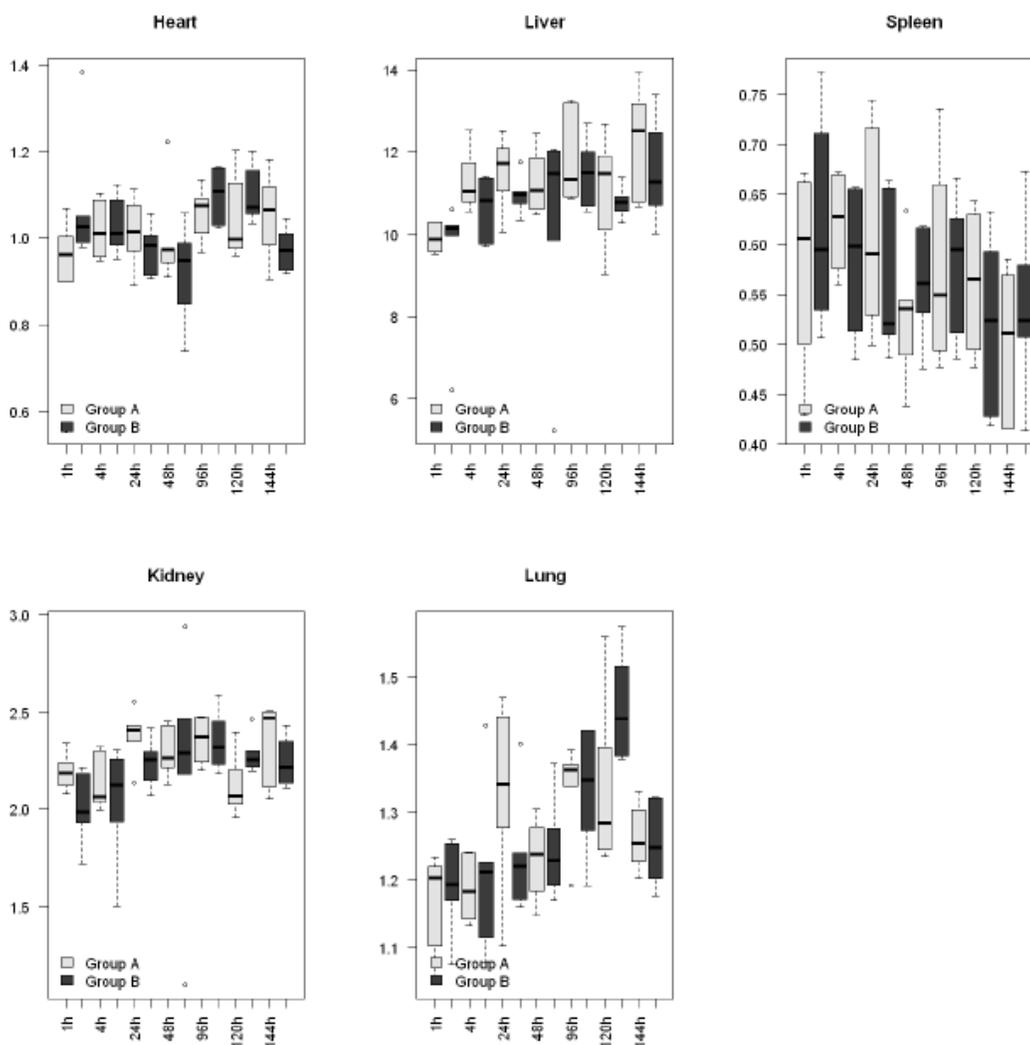


Figure 15: Mean Plasma Concentrations (N = 6/timepoint) of Total Doxorubicin in Male Rats following a single IV (1 mg/kg) dose of Doxil[®]

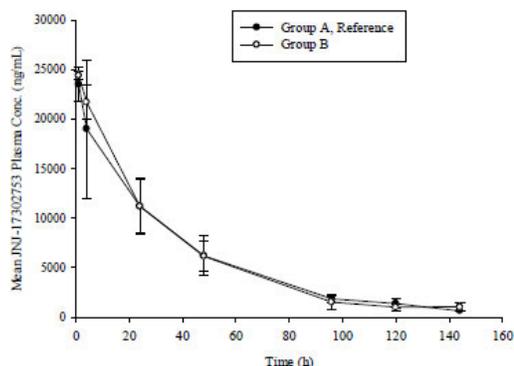


Table 11: Summary of plasma exposures

Parameter		Ratio ^a	90% CI limits
AUC _{0-144h}	Plasma	1.02	0.90-1.16
AUC _{0-∞}	Plasma	1.03	0.92-1.17

^a ratio of mean group B value to mean group A value.

Table 12: Summary of tissue exposures

Parameter	Tissue	Ratio ^a	90% CI limits
AUC _{0-144h}	Heart	0.79	0.69-0.91
	Kidney	0.91	0.81-1.02
	Liver	1	0.91-1.11
	Lung	1.26	1.07-1.51
	Spleen	1.12	1.00-1.26
Parameter	Tissue	Ratio ^a	90% CI limits
AUC _{0-∞}	Heart	0.89	0.80-1.01
	Kidney	0.87	0.66-1.20
	Liver	1.03	0.92-1.16
	Lung	1.63	1.35-1.98
	Spleen	1.12	0.99-1.27

^a ratio of mean group B value to mean group A value.

Bolded: outside the reference limits: 0.80-1.25

Figure 16: Mean Heart Concentrations (N = 6/timepoint) of Total Doxorubicin in Male rats following a single IV (1 mg/kg) dose of Doxil®

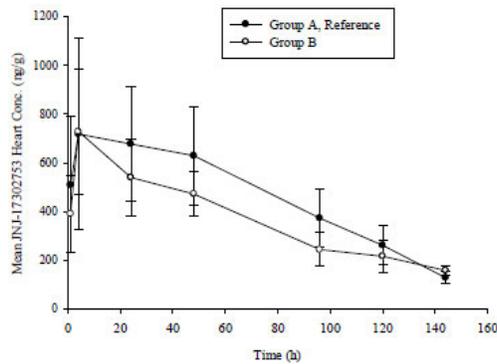


Figure 17: Mean Kidney Concentrations (N = 6/timepoint) of Total Doxorubicin in Male rats following a single IV (1 mg/kg) dose of Doxil®

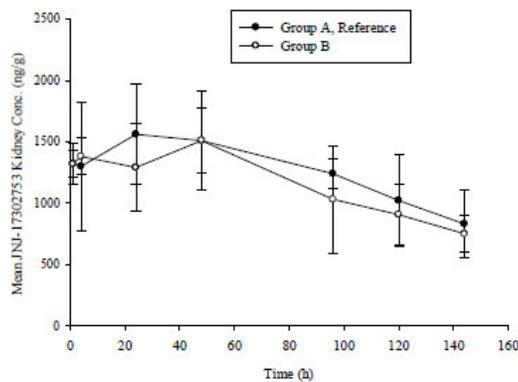


Figure 18: Mean spleen concentrations (N = 6/timepoint) of total doxorubicin in male rats following a single IV (1 mg/kg) dose of Doxil®

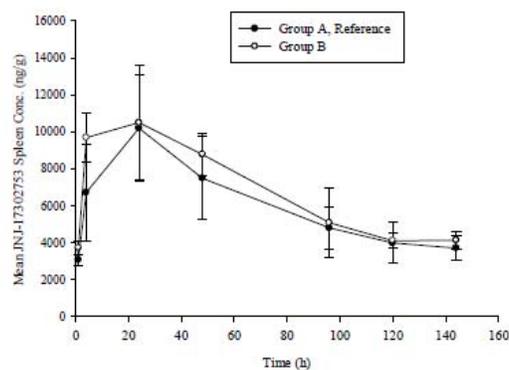


Figure 19: Mean lung concentrations (N = 6/timepoint) of total doxorubicin in male rats following a single IV (1 mg/kg) dose of Doxil®

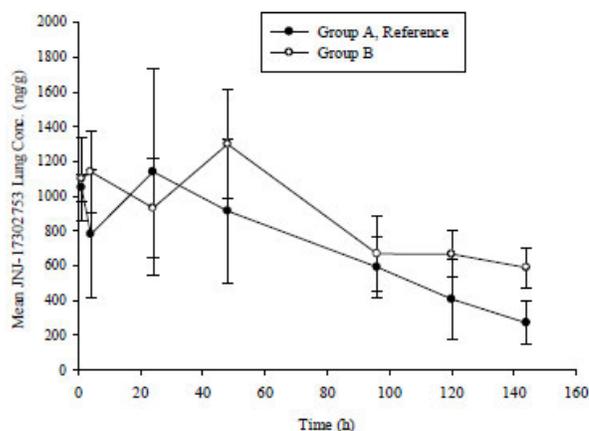
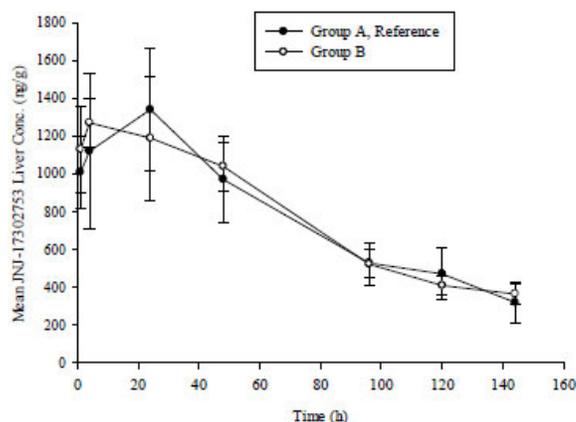


Figure 20: Mean liver concentrations (N = 6/timepoint) of total doxorubicin in male rats following a single IV (1 mg/kg) dose of Doxil®



The Sponsor concluded that, on the basis of overall PK similarity, which met the criteria for bioequivalence and on the basis of the overall similarity in tissue distribution between the BVL and TTY sources, the materials should be considered bioequivalent.

While it is agreed that bioequivalence is a property of PK similarity and not tissue distribution, and that on those grounds, these materials were bioequivalent in the rat, it is not agreed that a study in the rat is sufficient to demonstrate clinical bioequivalence. For that reason, these data will not be considered sufficient to grant a waiver of clinical bioequivalence testing for material supplied by the TTY facility.

Study title: JNJ-17302753-AAC: Pharmacokinetics and Tissue Distribution of Doxorubicin in the Male Mouse after Single Intravenous Bolus Dose Administration of Doxorubicin HCl Liposome Injection at 6 mg/kg

Study no.: TOX10507
Study report location: 4.2.2.2
Conducting laboratory and location: (b) (4) Beerse site
Turnhoutseweg 30
B-2340 Beerse, Belgium
Date of study initiation: Not stated
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Group A: BVL Batch 1207168
Group B: TTY Batch DCXIA1201

Methods

Doses: 6 mg/kg
Frequency of dosing: Single dose
Route of administration: IV (tail vein)
Dose volume: 10 mL/kg
Formulation/Vehicle: Clinical formulation diluted in 5.5% dextrose
Species/Strain: Mouse, SPF albino Swiss
Number/Sex/Group: 6M/timepoint
Age: Approximately 4 weeks upon arrival
Weight: 24-31 grams on the first day of dosing
Satellite groups: None
Unique study design: Tissue Distribution
Deviation from study protocol: Unknown

As illustrated in Sponsor-Table 13 and Sponsor-Figure 23, plasma concentrations achieved with the BVL and TTY two lots of material were similar enough to be considered bioequivalent (within the range of the 90% confidence limits (0.80-1.25) of the reference article). Not all tissues, however, met the criteria for bioequivalence, as indicated in Sponsor-Table 14 and in Sponsor-Figure 24 through Sponsor-Figure 28, as the mean exposure ratios for the heart, lung, and spleen fell outside the pre-specified confidence intervals.

The Sponsor concluded that, on the basis of overall PK similarity, which met the criteria for bioequivalence and on the basis of the overall similarity in tissue distribution between the BVL and TTY sources, the materials should be considered bioequivalent.

Table 13: Summary of Plasma Bioequivalence Findings

Parameter		Data Set with 2 outliers ^a		Data Set without 2 outliers ^a	
		Ratio ^b	90% CI limits	Ratio ^b	90% CI limits
AUC _{0-144h}	Plasma	1.00	0.88-1.15	0.97	0.89-1.06
AUC _{0-∞}	Plasma	1.00	0.89-1.13	0.97	0.90-1.05

^a Two animals (014M and 119F, one each group) considered outlier based on very low plasma and all tissues at the corresponding time points

Table 14: Summary of Tissue Bioequivalence Findings

Parameter	Tissue	Data Set with 2 outliers ^a		Data Set without 2 outliers ^a	
		Ratio ^b	90% CI limits	Ratio ^b	90% CI limits
AUC _{0-144h}	Heart	0.91	0.78 -1.06	0.91	0.81-1.01
	Kidney	1.06	0.96-1.18	1.06	1.01-1.12
	Liver	0.95	0.84-1.07	0.93	0.86-1.01
	Lung	1.13	1.0- 1.28	1.15	1.06-1.25
	Spleen	0.70	0.59 -0.83	0.71	0.62 -0.81
AUC _{0-∞}	Heart	1.00	0.86-1.16	0.96	0.85-1.07
	Kidney	0.92	0.82-1.03	0.92	0.84-1.01
	Liver	0.97	0.87-1.08	0.94	0.87-1.02
	Lung	1.27	1.02- 1.56	1.21	1.03- 1.42
	Spleen	0.80	0.65 -0.96	0.81	0.67 -0.96

^a Two animals (014M and 119F, one each group) considered outlier based on very low plasma and all tissues at the corresponding time points

^b ratio of mean group B value to mean group A value.

Bolded: outside the reference limits: 0.80-1.25

Figure 21: Comparison of mean exposures (AUC_{0-144h}) in plasma and tissues for the test (BVL) and reference (TTY) products

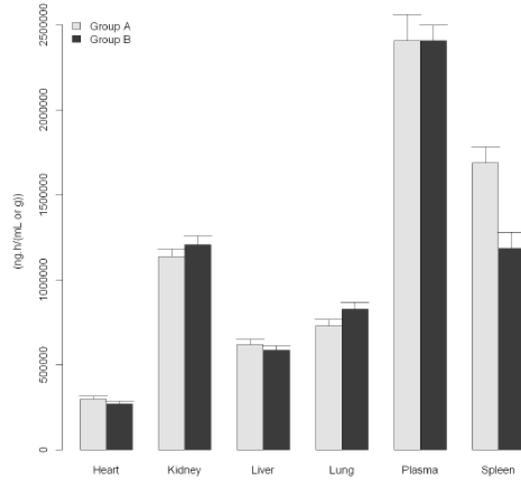


Figure 22: Comparison of mean exposures (AUC_{∞}) in plasma and tissues for the test (BVL) and reference (TTY) products

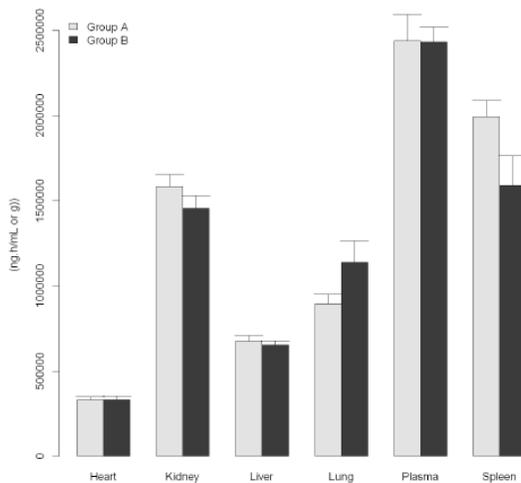


Figure 23: Mean plasma concentrations (N = 6/timepoint) of total doxorubicin in male mice following a single 6 mg/kg IV bolus injection of Doxil®

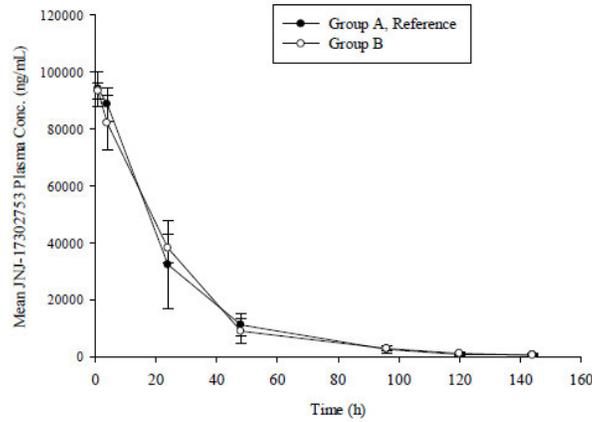


Figure 24: Mean heart concentrations (N = 6/timepoint) of total doxorubicin in male mice following a single 6 mg/kg IV bolus injection of Doxil®

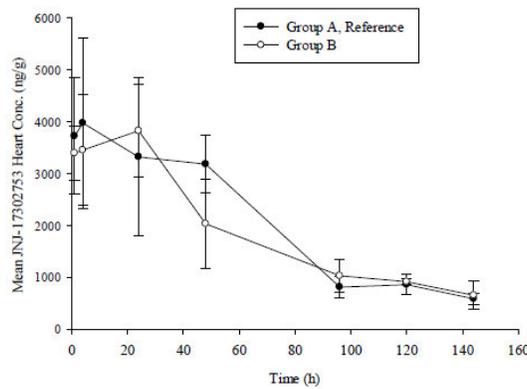


Figure 25: Mean spleen concentrations (N = 6/timepoint) of total doxorubicin in male mice following a single 6 mg/kg IV bolus injection of Doxil®

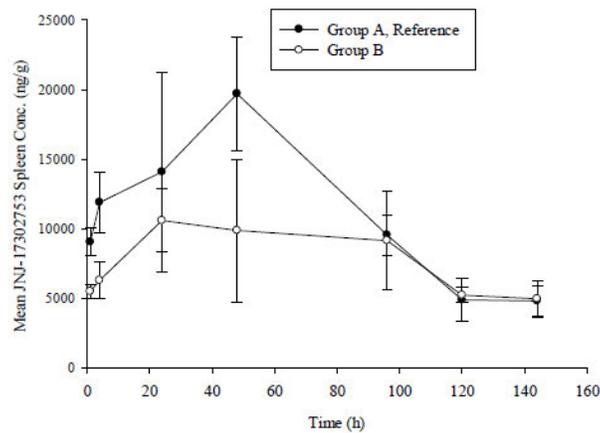


Figure 26: Mean kidney concentrations (N = 6/timepoint) of total doxorubicin in male mice following a single 6 mg/kg IV bolus injection of Doxil®

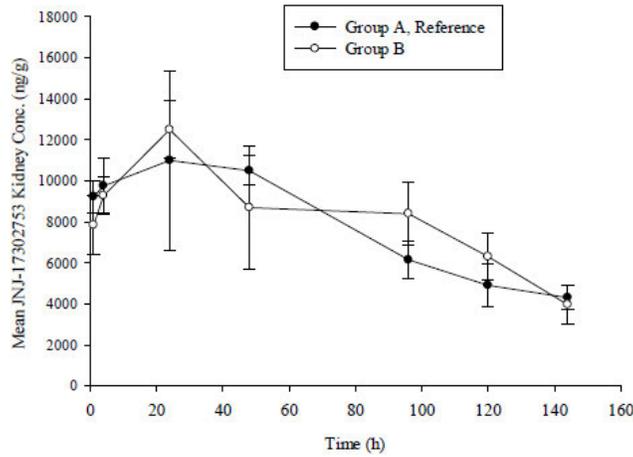


Figure 27: Mean lung concentrations (N = 6/timepoint) of total doxorubicin in male mice following a single 6 mg/kg IV bolus injection of Doxil®

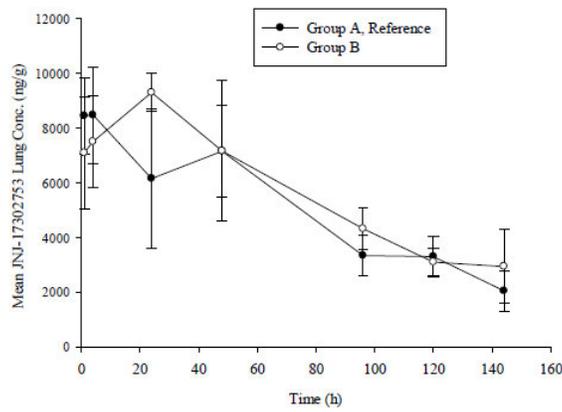
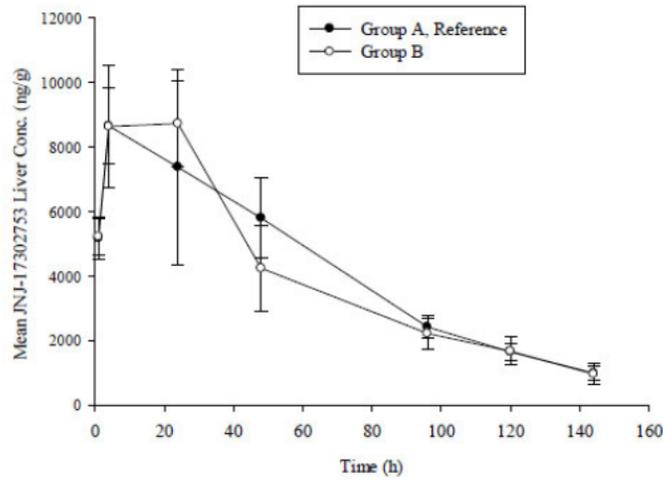


Figure 28: Mean liver concentrations (N = 6/timepoint) of total doxorubicin in male mice following a single 6 mg/kg IV bolus injection of Doxil®



10 Method Validation Reports



11 Integrated Summary and Safety Evaluation

This supplement was submitted to provide a nonclinical justification for waiving the requirement for bioequivalence with a change of manufacturing venue from Ben Venue (Ohio) to TTY (Taiwan). In support of this request, the Sponsor conducted numerous feasibility studies, in which they attempted to establish that bioequivalence could be demonstrated with administration of a single formulation to two groups of animals. They also evaluated both the IV bolus and IV infusion routes of administration.

On the basis of these preliminary studies, the Sponsor designed the definitive assays: an IV bolus study in the rat at a dose of 1 mg/kg, and an IV bolus study in the mouse at a dose of 6 mg/kg. In both studies, the criteria for bioequivalence were met on the basis of plasma exposures.

While on the basis of plasma exposures, the two sources of material achieved bioequivalence when administered by IV bolus injection to rats (1 mg/kg) and mice (6 mg/kg), they were not bioequivalent for tissue distribution kinetics. It should be noted, however, that distribution is not typically assessed for the purposes of bioequivalence testing, so the relevance of this observation is unclear.

Whatever differences were observed between suppliers in the distribution to normal tissues there appeared to be no effect on efficacy in tumor-bearing animals, as the two

sources appeared to behave comparably in mouse breast adenocarcinoma xenografts. There were no differences between BVL and TTY in overall plasma exposure or in tissue distribution to tumors. There were also no differences in tumor growth suppression or tumor weight between the two treatment arms, at either dose evaluated.

The weight of evidence suggests that the two lots of material are bioequivalent in animals for the primary endpoint of overall plasma exposure, and for apparent distribution to tumors. The two lots differ with regard to biodistribution to normal organs; however, as this is not a parameter that is typically evaluated in bioequivalence studies, it is unclear what that observation signifies.

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/s/

SHAWNA L WEIS
08/22/2013

WHITNEY S HELMS
08/23/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

28 August 2013

NDA: 50-718/S-046

Drug Product Name

Proprietary: DOXIL[®]

Non-proprietary: Doxorubicin HCl liposome injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12 July 2013	12 July 2013	29 July 2013	02 August 2013
16 August 2013	16 August 2013	n/a	n/a
28 August 2013	28 August 2013	n/a	n/a

Submission History (for 2nd Reviews or higher): N/A

Applicant/Sponsor

Name: Janssen Products, LP

Address: 920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Representative: Naushad Islam, MS, R.Ph.
Director, Regulatory Affairs

Telephone: (908) 704-5145

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUBMISSION:** Prior Approval Supplement
- 2. SUBMISSION PROVIDES FOR:**
- Addition of a manufacturing site for the manufacturing process of the drug product - TTY Biopharm
 - Change in batch size of the drug product - (b) (4) for TTY
 - Change in the specification for the containers and closures for the drug product - use of (b) (4) stoppers
 - Addition of a secondary packaging site: (b) (4)
- 3. MANUFACTURING SITE:**
 TTY Biopharm Company Limited
 No. 838, Sec. 1, Chung Hwa Rd. (838 Zhōnghuá Road, Section 1)
 Chungli, Taoyuan, Taiwan, R.O.C. (Zhongli City Taoyuan, Taiwan, R.O.C.)
 FEI: 3005054986
 DUNS: 658865659
- Secondary Packaging site: (b) (4)
- 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Liposomal Injection for intravenous injection, 2mg/mL packaged as
- 20mg doxorubicin in 10 mL in a 10mL vial
 - 50mg doxorubicin in 25 mL in a 30mL vial
- (b) (4)
- The drug product is labeled as a "single use vial."
- 5. METHOD(S) OF STERILIZATION:** (b) (4)
- 6. PHARMACOLOGICAL CATEGORY:** Treatment of patients with AIDS-related Kaposi's sarcoma, Metastatic Carcinoma of the Ovary, and Multiple Myeloma
- B. SUPPORTING/RELATED DOCUMENTS:**
- DMF (b) (4) for the (b) (4) of the stopper.
 - Microbiology review of (b) (4)
- C. REMARKS:**
- This NDA supplement was provided in eCTD format.
 - Information requests (2) were sent on August 07 and 16, 2013.

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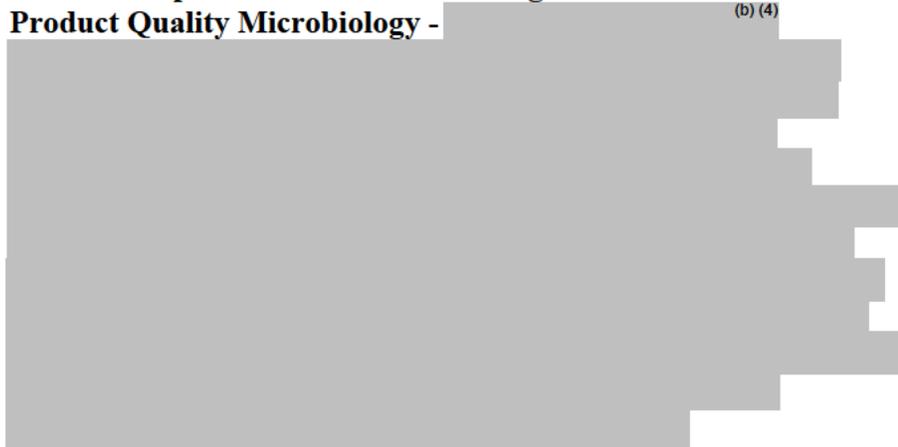
Executive Summary

I. Recommendations

- A. Recommendation on Approvability - Recommended for Approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** (b) (4)



- B. Brief Description of Microbiology Deficiencies - None.**
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**
- D. Contains Potential Precedent Decision(s)- Yes No**

III. Administrative

A. Reviewer's Signature: _____
Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block: _____
John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

C. CC Block
NDA 50718

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/s/

ROBERT J MELLO
08/29/2013

JOHN W METCALFE
08/29/2013
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

SUBMISISON	NDA 50-718 Supplement-46 (SDN 943)
BRAND NAME	DOXIL [®] for intravenous infusion
GENERIC NAME	Doxorubicin HCl liposome injection for intravenous infusion
DOSAGE FORM	DOXIL is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials
INDICATION	Ovarian Cancer: for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy AIDS-Related Kaposi's Sarcoma: for the treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy Multiple Myeloma: in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.
SUBMISSION DATES	January 9, 2015 (SDN 943)
SUBMISSION TYPE	Response to Information (RTI)
APPLICANT	Janssen Research and Development, LLC
OND DIVISION	Division of Oncology Products 2 (DOP2)
OCP DIVISION	Division of Clinical Pharmacology V (DCP V)
OCP REVIEWER	Safaa Burns, Ph.D.
OCP TEAM LEADER	Gene Williams, Ph.D.

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4. Appendices	5
4.1 Applicant's Proposed Labeling (July 12, 2013, SDN 883)	
4.2 FDA Labeling Sent to the Applicant (December 31, 2014)	

1. EXECUTIVE SUMMARY

This submission contains the Applicant's response to the FDA's proposed revisions to their

package insert that were communicated to the Applicant on December 31, 2014. The purpose of the current submission is to review the Applicant's response to these edits (see section 3 of this review). See Dr. Burns' review of October 25, 2013 for additional history of this application.

1.1 RECOMMENDATIONS

The applicant agreed on the clinical pharmacology edits made to Sections 2.6, 7, 8.6 and 12.3. We have no further recommendations.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

No new clinical pharmacology information was submitted to this supplemental NDA; there are no clinical pharmacology findings.

2 QUESTION BASED REVIEW

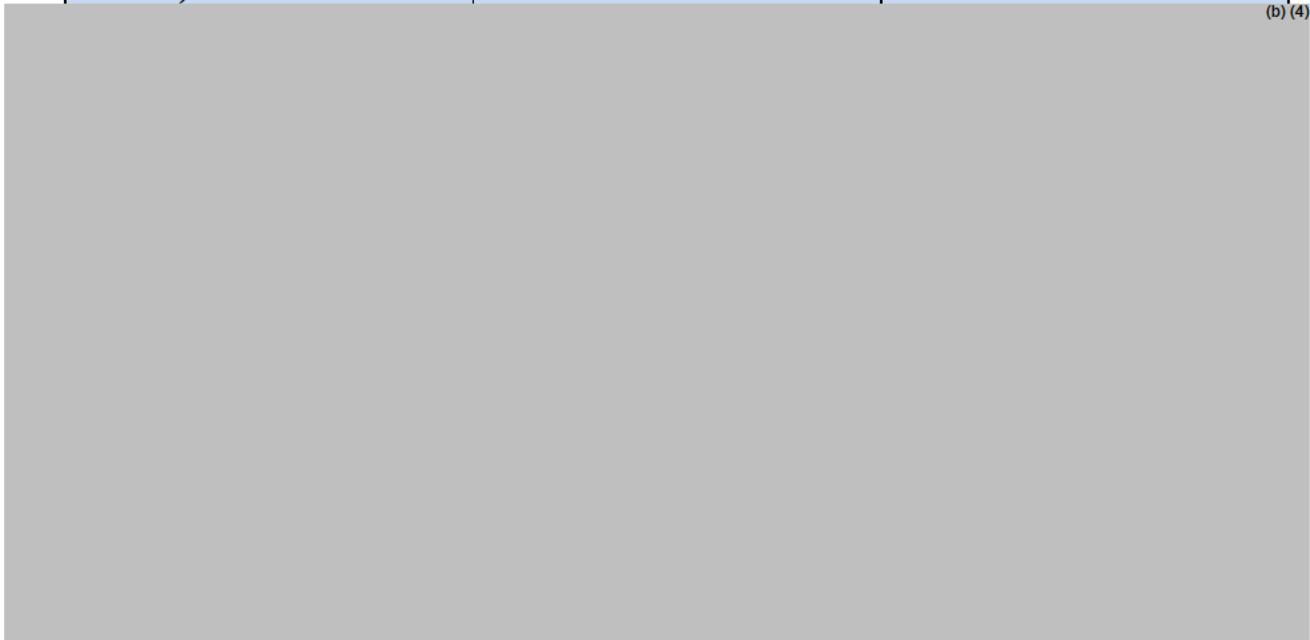
No new clinical pharmacology information was submitted to this supplemental NDA; no question based review was conducted.

3. DETAILED CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS

The reviewer's preliminary edits to the proposed package insert begin on the next page of this review. The starting point for the edits was the Applicant's originally proposed labeling version. The middle column represents the FDA edits that were sent to the sponsor on December 31, 2014 and right hand column represent the Applicant's response (current submission). The entirety of Applicant's proposed labeling submitted on July 12, 2013 (SDN 883) and the FDA's final edits sent to the Applicant on December 31, 2014 are attached to this review as Appendices 4.1 and 4.2, respectively.

Applicant's Proposed Labeling included in the PAS-CMC Supplement-46 (July 12, 2013, SDN 883)	FDA's Labeling Edits Sent to the Applicant on December 31, 2014	Applicant's Response to the FDA's Edits received on January 9, 2015 (SDN 943)
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(b) (4)



Appendices

4.1 Applicant's Proposed Labeling (July 12, 2013, SDN 883)

4.2 FDA Labeling Sent to the Applicant (December 31, 2014)

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/s/

SAFAA BURNS
01/13/2015

GENE M WILLIAMS
01/13/2015
I concur with the recommendations

CLINICAL PHARMACOLOGY REVIEW

SUBMISSION	NDA 50-718 Supplement-46 (SDN 883)
BRAND NAME	DOXIL [®] for intravenous infusion
GENERIC NAME	Doxorubicin HCl liposome injection for intravenous infusion
DOSAGE FORM	DOXIL is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials
INDICATION	Ovarian Cancer: for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy AIDS-Related Kaposi's Sarcoma: for the treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy Multiple Myeloma: in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.
SUBMISSION DATE	July 12, 2013
SUBMISSION TYPE	PAS (Prior Approval Supplement) CMC (Chemistry Manufacturing and Controls)
APPLICANT	Janssen Research and Development, LLC
OND DIVISION	Division of Oncology Products 2 (DOP2)
OCP DIVISION	Division of Clinical Pharmacology 5 (DCP 5)
OCP REVIEWER	Safaa Burns, Ph.D.
OCP TEAM LEADER	Gene Williams, Ph.D.

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- 4.1 Applicant's Proposed PLR Labeling
- 4.2 Approved Package Insert (August 30, 2013)

1. EXECUTIVE SUMMARY

The submission is a Prior Approval Supplement submitted primarily to address manufacturing (CMC) issues. The submission includes proposed changes to package insert language. Changes to package insert section **12.1 Mechanism of Action** were proposed, no changes to sections **7 DRUG INTERACTIONS** or **12.3 Pharmacokinetics** were proposed. No new clinical pharmacology information was submitted; the proposed changes to section **12.1** were not based on new clinical pharmacology information.

This review includes FDA proposed edits to the package insert. These edits occurred at an inter-disciplinary review team meeting that Dr. Williams (the secondary reviewer for this review) did not attend. Package insert language is not being negotiated with the applicant, as the application will not be approved due to CMC issues. As the proposed edits will not be conveyed, Dr. Williams has not reviewed them. The purpose of including the proposed edits is to prevent potential duplication of effort: if desired by the subsequent clinical pharmacology primary and secondary reviewers, the edits can be considered when the application is re-submitted.

To enhance review of any re-submission, the review team (all review disciplines) is forwarding general recommendations regarding package insert language to the applicant. Because the proposed edits included in this review are not of a general nature, this reviewer has no proposed edits to be conveyed to the applicant.

1.1 RECOMMENDATIONS

We have no recommendations.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

No new clinical pharmacology information was submitted to this supplemental NDA; there are no clinical pharmacology findings.

2 QUESTION BASED REVIEW

No new clinical pharmacology information was submitted to this supplemental NDA; no question based review was conducted.

3. DETAILED CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS

The review team's preliminary edits (see **1. EXECUTIVE SUMMARY** for a background regarding the origin of these edits) to the proposed package insert begin on the next page of this review. The starting point for the edits was the applicant's proposed version. Portions that indicate a change was made (vertical line on the left), but lacking observable changes (no ~~strikeouts~~ or additions) are an artifact of what was provided by the applicant – this reviewer made no changes to those portions. The entirety of the applicant's proposed package insert and the approved package insert version of (August 30, 2013) are appended to this review (**Appendices 4.1** and **4.2**, respectively).

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/s/

SAFAA BURNS
10/25/2013

GENE M WILLIAMS
10/25/2013

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	50-718/S-046
Submission Date:	7/12/2013
Brand Name:	Doxil Injection
Generic Name:	Doxorubicin HCl Liposome Injection
Formulation:	Liposomal Suspension for Injection
Strength:	20 and 50 mg vials at concentration of 2 mg/mL
Applicant:	Janssen
Reviewer:	John Duan, Ph.D.
Submission Type:	New Manufacturing Site

BACKGROUND

The Submission: The current submission includes a prior approval supplement for an additional facility, TTY Biopharm located in Taiwan for the manufacture of DOXIL. DOXIL is currently manufactured at Ben Venue Laboratories (BVL) in Bedford, OH. The Applicant intends to manufacture DOXIL at the new facility using the same process as BVL. Note that a bioequivalence study protocol to support the approval of this new site was submitted and reviewed by the FDA. However, in this submission the Applicant is requesting a waiver of the requirement to submit the data from this bioequivalence study.

The Review: The review is focused on the evaluation and acceptability of the biowaiver request.

RECOMMENDATION

From the Biopharmaceutics perspective, a Complete Response is recommended. The following comments should be conveyed to the Applicant.

COMMENTS TO BE CONVEYED TO THE APPLICANT

1. As already conveyed to you during the teleconference held on 7/25/2013, your request for a biowaiver is NOT acceptable. To qualify the new manufacturing site at TTY, Taiwan, a bioequivalence (BE) study is necessary. A BE study conducted in an animal model cannot substitute the human BE study. You should conduct the bioequivalence study as planned per the study protocol (DOXILNAP1002).
2. In section "3.2.P.2.3 Manufacturing Process Development," the in vitro drug leakage and in vitro drug release assay under multiple pH conditions were assessed. However, the sample sizes, the variability in each test, the data for each individual unit and the similarity factor f2 values were not provided. Submit the following information.
 - a. The sample sizes and individual data with the variability (standard deviation and/or CV) for each lot used in each of the drug leakage and the in vitro drug release tests.

- b. The similarity factor f_2 values for the profile comparisons using ^(b)₍₄₎ units of each lot per test.
3. Implement the newly approved in vitro drug release method (Lutidine method DS-TMD-4822) and acceptance criteria. Provide the revised specification table for your drug product with these updates.

John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Angelica Dorantes, Ph.D.
Team Leader
ONDQA Biopharmaceutics

cc: NDA 50-718 (S-046)/DARRTS, RLostritto

Appendix

BIOPHARMACEUTICS ASSESSMENT – REVIEWER NOTES

I. Background

The current submission includes a prior approval supplement for an additional facility, TTY Biopharm located in Taiwan for the manufacture of DOXIL. DOXIL is currently manufactured at Ben Venue Laboratories (BVL) in Bedford, OH. The Applicant intends to manufacture DOXIL at the new facility using the same process as BVL. The submission contains Chemistry Manufacturing and Controls as well as Non Clinical information. A waiver for the requirement to submit the BE study is being requested in the current submission. The regulatory history related to the currently submitted biowaiver request is briefly summarized below.

The proposed long term solution for the drug shortage of Doxil was to manufacture the product at an entirely new manufacturing facility. Several meetings and correspondences have occurred over the past year with respect to the long term solution. These include a teleconference on August 21, 2012, discussing the draft protocol element design (PED) for a bioequivalence (BE) study to support the long term solution; a revised PED provided by Janssen on September 13, 2012; a letter the FDA issued on November 21, 2012; Janssen's responses to the FDA letter on December 5, 2012; an informal, non-PDUFA tracked teleconference held on December 11, 2012.

The December 11, 2012, teleconference had the following action items: (1) Janssen agreed to provide clarification on which lots would be used for the BE study. Following review of the information to be submitted by Janssen, FDA agreed to provide a response to Janssen regarding whether the use of this material would be acceptable for the BE study; and, (2) Janssen agreed to submit the final protocol for the BE study to IND 36778 for FDA to review and comment on.

Janssen submitted an amendment dated December 20, 2012, which contained the BE protocol as discussed during the December 11, 2012, teleconference, DOXILNAP1002 entitled, "A Pivotal Bioequivalence Study of DOXIL/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies including Subjects with Ovarian Cancer." This BE study is based on encapsulated and unencapsulated ("free") doxorubicin.

The FDA made several comments on the proposed protocol in an advice/information request letter issued on 1/11/2013.

IND (eCDT-534) was submitted on 3/20/2013 providing the revised protocol in support of a proposed new manufacturing facility for Doxil at TTY Biopharm Co in Chungli Taoyuan, Taiwan.

After reviewing the protocol, FDA issued a memorandum on 5/24/2013, with comments on certain non-hold issues. The submission (eCDT-546) dated 5/29/2013 provides the responses to the non-hold issues.

II. Evaluation of the Biowaiver Request

The Applicant submitted a biowaiver request in this submission based on the following.

TTY Biopharm (TTY) is proposed as an additional manufacturing site for the drug product for commercial production at a (b) (4) scale. Some changes to equipment and the process were made to transfer the manufacturing process for drug product to TTY. The Applicant claimed that most changes were related to scale (batch size of (b) (4) for BVL and batch size of (b) (4) for TTY), and most critical process parameters (CPP) were not impacted by the process changes. There were no changes in raw materials utilized for production at TTY associated with an identified critical material attributes (CMA). Furthermore, the batch release, characterization, and stability data and nonclinical assessment of the finished product demonstrated equivalency between drug products manufactured at BVL/ (b) (4) and TTY.

In addition to physicochemical comparability, the Applicant performed a non-clinical evaluation to support equivalence between the TTY and reference batches. The nonclinical evaluation demonstrated that product manufactured at TTY is bioequivalent to the reference batch. This conclusion is based on demonstrating equivalency for efficacy in a tumor mouse model, equivalency in plasma pharmacokinetics and tissue distribution in normal mice, rats and in a tumor mouse model.

Due to the current compliance situation at BVL, that resulted in supply constraints, and BVL's own plan to discontinue contract manufacturing of DOXIL, Janssen requests a waiver from performing a BE study in order to bring DOXIL back to the market as quickly as possible in order to ensure a stable supply.

Reviewer's Comments: The Biowaiver requested cannot be granted. To qualify the new manufacturing site at TTY, a bioequivalence (BE) study is necessary. An animal study cannot substitute the human BE study. The Applicant should conduct the BE study as planned.

III. In vitro release profile comparison

1. In Vitro Drug Leakage under Stress Conditions

In Vitro Drug Leakage was assessed under the following conditions.

A. The presence of 50% human plasma, to evaluate liposome stability in blood circulation

(b) (4) HLB solid phase extraction cartridges (b) (4)
re separated by (b) (4)
. As indicated in Table 1 there is little indication of leakage of doxorubicin at the time points tested in the presence of 50% of human plasma. This is true for both BVL and TTY samples.

Table 1: Drug Leakage in the Presence of 50% Human Plasma

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	0.2	0.4	0.1
	TTY	0.0	-0.4	-0.2	-0.6

B. As a function of pH (5.5, 6.5, and 7.5) to mimic drug release in normal tissues, around cancer cells, or inside cancer cells, respectively

Table 2, Table 3 and Table 4 summarize the results from both manufacturers for drug leakage after incubation at pH 5.5, 6.5, and 7.5, respectively. There is little indication of leakage at the time points tested at the three pH values for both BVL and TTY samples.

Table 2: Drug Leakage after Incubation at pH=5.5

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	0.3	0.4	0.4
	TTY	0.0	0.1	-0.5	-0.4

Table 3: Drug Leakage after Incubation at pH=6.5

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	0.6	0.6	0.4
	TTY	0.0	-0.4	-0.5	-0.6

Table 4: Drug Leakage after Incubation at pH=7.5

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	-0.2	0.2	-0.1
	TTY	0.0	-0.2	-0.9	-0.7

C. As a function of temperature (43 °C, 47 °C, 52 °C, and 57 °C) to evaluate the lipid bilayer integrity

Table 5, Table 6, Table 7 and Table 8 summarize the results from both manufacturers for drug leakage after incubation at 43, 47, 52, and 57 °C respectively. At 43 °C, there is no discernible leakage at the time points tested, and at elevated temperatures (47, 52, or 57 °C) there is a small amount of leakage. The batches from BVL and TTY perform similarly in this test at the conditions tested.

Table 5: Drug Leakage after Incubation at Temperature = 43 °C

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	0.9	0.6	1.0
	TTY	0.0	1.5	0.0	-0.3

Table 6: Drug Leakage after Incubation at Temperature = 47 °C

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	1.5	3.4	3.2
	TTY	0.0	3.1	2.3	-0.1

Table 7: Drug Leakage after Incubation at Temperature = 52 °C

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	1.6	1.4	2.4
	TTY	0.0	2.9	-0.1	0.1

Table 8: Drug Leakage after Incubation at Temperature = 57 °C

Manufacturer		% Leakage			
		t = 0	t = 2 hour	t = 4 hour	t = 24 hour
Mean	BVL	0.0	1.7	2.1	1.8
	TTY	0.0	2.6	1.7	0.6

D. Exposure to low frequency ultrasound (20 kHz) to evaluate the state of encapsulated drug in the liposome

E. Table 9 summarizes the results from both manufacturers for drug leakage after exposure to low frequency ultrasound for 0, 5, 10, 30, and 60 minutes. There is an indication of a steady release over time as illustrated in

F.

Figure 1 for the individual TTY batches versus the mean for the BVL batches. The release curves are similar for the various samples, and indicate that the TTY batches have similar leakage properties to the BVL reference batches when exposed to ultrasound.

Table 9: Drug Leakage after Exposure to Ultrasound

Manufacturer		% Leakage				
		t = 0	t = 5 min	t = 10 min	t = 30 min	t = 60 min
Mean	BVL	0.0	28.3	46.6	75.8	85.6
	TTY	0.0	26.1	42.6	72.5	84.1

Figure 1: Percent of Drug Leakage after Exposure to Low Frequency Ultrasound (b) (4)



Reviewer's Comments: The in vitro drug leakage data under stressed conditions show the similarity between the two manufacturing sites. However, the sample sizes used and the variability in each test were not provided. In addition, the data for individual units were not provided. The complete data should be provided for review.

2. In Vitro Drug Release Assay under Multiple pH Conditions using Lutidine Buffer

This testing was performed at two conditions (at 37 °C with pH 5.5, 6.5, and 7.5, and at 39 °C with pH 6.7) for samples from TTY and BVL.

A. At 37°C with pH 5.5, 6.5, and 7.5

A sample is placed in 2,6-lutidine citrate buffer at 37 °C at pH 5.5, 6.5, or 7.5 to elicit doxorubicin release from the liposomes. The amount of drug released during the assay is quantified using fluorescence detection. A release profile is constructed with time points taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 24 hours. A 0-hour sample is prepared and measured to correct for the low level of fluorescence intensity of encapsulated drug. An infinity sample, consisting of full drug release from the liposomes, is prepared by heating the sample at 72 °C for 0.5 h in 2,6-lutidine buffer. The percent drug release at the individual time points is calculated using the following equation:

$$\% \text{ Drug release} = 100 * \frac{(\text{Sample}_{\text{Emission Intensity}} - 0 \text{ hr}_{\text{Emission Intensity}})}{(\text{Infinity}_{\text{Emission Intensity}} - 0 \text{ hr}_{\text{Emission Intensity}})}$$

Where $\text{Sample}_{\text{Emission Intensity}} = \text{Fluorescence Intensity at the time point}$

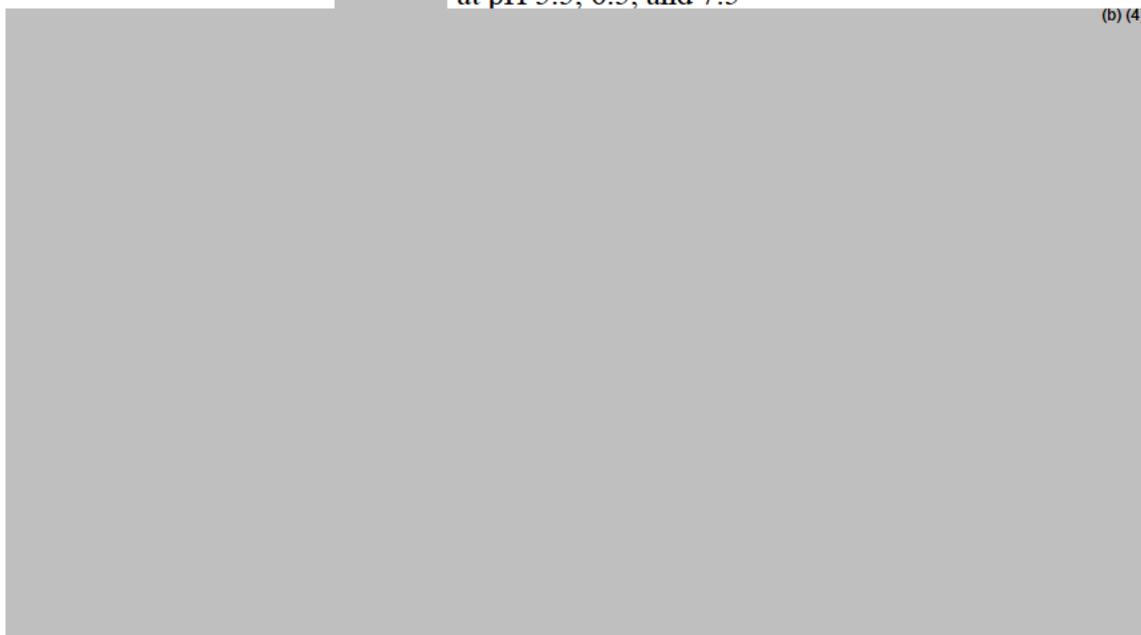
$0 \text{ hr}_{\text{Emission Intensity}} = \text{Fluorescence Intensity of an initial sample prior to release assay}$

$\text{Infinity}_{\text{Emission Intensity}} = \text{Fluorescence Intensity of a sample heated at } 72^{\circ}\text{C} \text{ for } 100\% \text{ drug release}$

(b) (4) TTY batch (b) (4) was compared versus (b) (4) BVL batch (b) (4) at pH 5.5, 6.5, and 7.5. Data were measured at 0.25, 0.5, 1, 2, 3, 4, 6, and 24 hours at pH 5.5 and 6.5, and at 0.25, 0.5, 1, 1.5, 2, 3, and 4 hours at pH 7.5.

Figure 2 shows the average of 12 individual vials for each batch at each pH. The sponsor concluded that the TTY batch (b) (4) is equivalent to BVL batch (b) (4) in performance in this lutidine buffer release assay.

Figure 2: In Vitro Drug Release Comparison of TTY Batch (b) (4) and BVL Batch (b) (4) at pH 5.5, 6.5, and 7.5



B. At 39°C and pH 6.7

To further evaluate the release profile of multiple batches from TTY and BVL (b) (4), the sample is placed in a 2,6-lutidine citrate buffer at 39 °C and pH 6.7 to elicit doxorubicin release from the liposomes. A release profile is constructed with time points taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, and 6 hours using the same method described in A section.

The (b) (4) TTY batches were compared against (b) (4) BVL batches ((b) (4)) and data were measured at 0.25, 0.5, 1, 2, 3, 4, and 6 hours. The data presented in

Figure 3 were generated from a single vial from each batch. Due to the similarity of the release profiles between the TTY and BVL batches, it is concluded that the products are equivalent.

Figure 3: In Vitro Drug Release Comparison of TTY and BVL Batches at pH 6.7 and 39 °C ^{(b) (4)}



Reviewer's Comments: *It seems that the release profiles at 37°C with pH 5.5, 6.5, and 7.5 and at 39°C and pH 6.7 are very similar. However, the following deficiencies are noted.*

- 1) *The f2 values for the profile comparisons, and the individual and the variability data were not provided. These data should be included in the to-be-submitted supplement.*
- 2) *The sponsor should be informed that the profile comparison at 39°C and pH 6.7 must use ^{(b) (4)} dosage units for each lot.*

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/s/

JOHN Z DUAN
09/19/2013

ANGELICA DORANTES
09/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

OTHER REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 22, 2015
From: Anuja Patel, M.P. H., Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 50718/S-046 Resubmission of Complete Response- FDA Agreed Labeling following teleconference held January 22, 2015

Please find attached FDA labeling revisions as agreed by Janssen representatives during the labeling teleconference held today between FDA and Janssen representatives at 7:30 A.M, EST.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA agreed upon revisions to the package insert

29 page(s) has been Withheld in Full as draft labeling (CCI/TS)
immediately following this page

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/s/

ANUJA PATEL
01/22/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 17, 2015
From: Anuja Patel, M.P. H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 50718/S-046 FDA Proposed Edits and Comments to Doxil Package
Insert following January 14 and 16, 2015, teleconferences

Dear Mr. Scurato,

We refer to our preliminary proposed revisions to the package insert (PI) and carton and container labeling sent via electronic mail (e-mail) on December 31, 2014, and acknowledge receipt of your January 9, 2015, response containing your proposed revisions to the PI and revised carton container.

In addition, we also refer to the teleconferences held on January 14 and 16, 2015, between FDA and Janssen to discuss and reach agreement on the proposed revisions to the Doxil PI.

We acknowledge receipt of your January 16, 2015, submission which contained your response to our information requests discussed during the January 14, 2015, teleconference. Please note, your January 16, 2015, submission is currently under review.

Please find attached FDA's proposed revisions and additional comments in the attached Doxil PI as discussed and agreed upon by Janssen during the teleconferences held on January 14 and 16, 2015, and additional minor revisions made by the review team following the teleconference.

In addition, for any revisions during made within the last year to sections in **BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS**, therefore we are requesting that you include a vertical line next to those sections in the full prescribing portion of the Doxil package insert.

Please provide a response to FDA's attached proposed revisions by 3:00 PM on Monday, January 19, 2015. In addition to submitting your response formally to the NDA, please email me a copy of your final agreed labeling.

Feel free to contact me if you have any questions.

Regards,

Anuja Patel, M.P.H.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment: FDA proposed revisions to the Doxil package insert

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/s/

ANUJA PATEL
01/17/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information**

Memorandum

Date: 01/16/2015

To: Anuja Patel, MPH
Senior Regulatory Project Manager
Division of Oncology Products 2 (DOP2)

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Through: Jessica Cleck Derenick, PhD
Team Leader
Office of Prescription Drug Promotion

Subject: **DOXIL[®] (doxorubicin HCL liposomal injection) for intravenous infusion**
NDA 050718/S-046
Office of Prescription Drug Promotion Comments on proposed labeling (PI and carton/container)

Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) and the carton/container labeling (carton label) for Doxil[®] (doxorubicin HCL liposomal injection) for intravenous infusion as requested in consult from DOP2 dated 10/27/14.

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "FDA 12.31.2014 Proposed Edits to Sponsor CLEAN" sent via electronic mail on January 5, 2015 to OPDP from DOP2 (Anuja Patel).

OPDP's review of the proposed carton label is based on the carton label draft titled, "50mg carton 109290500_7.pdf" sent via electronic mail on January 11, 2015 to OPDP from DOP2 (Anuja Patel).

OPDP has no comments on the proposed PI and carton label at this time.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
01/16/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

**Division of Pediatric and Maternal Health
Addendum to November 24, 2014 Review**

Date: December 22, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Carrie Ceresa, Pharm D., MPH,
Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 2 (DOP2)

Drug: Doxil (doxorubicin hydrochloride liposome injection)

NDA: 50718/Supplement-46

Applicant: Janssen Products, LP

Subject: Pregnancy and Nursing Mothers Labeling

In a review dated November 24, 2014, the Division of Pediatric and Maternal Health (DPMH) provided suggested revisions and structuring of existing information related to the Pregnancy and Lactation labeling for Doxil (doxorubicin hydrochloride) injection in order to provide clinically relevant information for prescribing decisions and to comply with the current regulatory requirements. See the prior DPMH Doxil memo for the previous version of Doxil labeling.¹

¹ DPMH Doxil review, November 24, 2014, DARRTS Reference ID 3661775

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”² also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule³ format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will officially take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format. DPMH refers to the final NDA action for final labeling, which included the PLLR format. See below for current Doxil labeling that has been placed into PLLR format.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- Embryofetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception (b) (4) 8.1, 8.3)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Discontinue breastfeeding. (8.2).

Warnings and Precautions

5.6 Embryofetal Toxicity

Based on animal data, DOXIL can cause fetal harm when administered to a pregnant woman. At doses approximately 0.12 times the recommended clinical dose, DOXIL was embryotoxic and abortifacient in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during (b) (4) [see *Use in Specific Populations* (8.1) and (8.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4), DOXIL can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, DOXIL was embryotoxic in rats and abortifacient in rabbits following intravenous administration during organogenesis at doses approximately 0.12 times the recommended clinical dose [see *Data*]. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

² *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

³ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

The background risk of major birth defects and miscarriage for the indicated populations is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal data

DOXIL was embryotoxic at doses of 1 mg/kg/day in rats and was embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about 0.12 times the recommended dose of 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.2 Lactation

It is not known whether DOXIL is present in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue nursing during treatment with DOXIL.

8.3 Females and Males of Reproductive Potential

Contraception

Females

DOXIL can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during [REDACTED] (b) (4)

Males

DOXIL may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and for 6 months after treatment with DOXIL [see *Nonclinical Toxicology (13.1)*].

Infertility

Females

In females of reproductive potential, DOXIL may cause infertility and result in amenorrhea [REDACTED] (b) (4). Premature menopause can occur with doxorubicin HCl. Recovery of menses and ovulation is related to age at treatment.

Males

DOXIL may result in oligospermia, azospermia, and permanent loss of fertility. Sperm counts have been reported to return to normal levels in some men. This may occur several years after the end of therapy [see *Nonclinical Toxicology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider with a known or suspected pregnancy [see *Warnings and Precautions* [REDACTED] (b) (4) and *Use in Specific Populations 8.1*].

- Advise females and males of reproductive potential to use effective contraception during and for 6 months following treatment with DOXIL. [see *Use in Specific Populations (8.3)*].

Lactation

- Advise females not to breastfeed during treatment with DOXIL [see *Use in Specific Populations (8.2)*].

Infertility

- Advise females and males of reproductive potential that DOXIL may cause temporary or permanent infertility [see *Use in Specific Populations (8.3)*].

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/s/

MIRIAM C DINATALE
12/22/2014

CARRIE M CERESA
12/22/2014

LYNNE P YAO
12/29/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: November 20, 2014 **Date consulted:** October 28, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Alyson Karesh, MD, Acting Team Leader, Maternal Health
Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 2 (DOP2)

Drug: Doxil (doxorubicin hydrochloride liposome injection)

NDA: 50718/Supplement-46

Applicant: Janssen Products, LP

Subject: Pregnancy and Nursing Mothers Labeling

Materials

Reviewed:

- DPMH consult request dated October 28, 2014, DARRTS Reference ID 3649410
- Sponsor's submitted background package for NDA 50718/S-046, Doxil
- Doxorubicin HCl labeling from drugs@fda accessed November 3, 2014, website: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050718s0451bl.pdf
- DPMH Review, Doxorubicin, NDA 50467, 50629, March 13, 2013, DARRTS Reference ID 3276351
- Division Director Summary Review, NDA 50718/S-46, November 11, 2013, DARRTS Reference ID 3404902
- Pharmacology/Toxicology NDA Review, NDA 50718, July 12, 2013. DARRTS Reference ID 3358834

Consult Question:

DOP2 requests DPMH assistance with pregnancy and nursing mothers labeling for an NDA supplement.¹

REGULATORY HISTORY

Doxil (doxorubicin hydrochloride (HCl) liposome injection, 505(b)(1) New Drug Application (NDA) 50718) is a cytotoxic anthracycline topoisomerase inhibitor that binds to DNA and inhibits nucleic acid synthesis. Doxil is approved for the following indications:

- Treatment of acquired immune deficiency syndrome (AIDS)-related Kaposi's Sarcoma in patients with disease that has progressed on prior combination chemotherapy or intolerance to such therapy - approved November 17, 1995
- Treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy- approved June 28, 1999
- Treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy- approved May 17, 2007²

On July 12, 2013, Janssen Products, LP submitted a CMC Supplement NDA (NDA 50718, supplement 46) under section 505 (b)(1) for Doxil requesting approval of a new manufacturing site and requesting a waiver from the requirement of conducting a bioequivalence study in patients.³

On November 12 2013, the FDA sent Janssen a Complete Response (CR) Letter to the CMC Supplement due to the lack of a bioequivalence study in humans. Although the FDA pharmacology/ toxicology reviewer concluded that the nonclinical bioequivalence data demonstrated bioequivalence in animals, these conclusions could not be extrapolated to humans. The FDA noted that using animal data (as Janssen had done) to meet the bioequivalence requirement was inadequate. The FDA required submission of results of bioequivalence studies done in patients with solid tumors, including patients with ovarian cancer, before the new manufacturing site could be approved.⁴ In addition, the FDA recommended that Janssen update drug labeling to conform to current doxorubicin HCl labeling (NDA 50467, NDA 50629), which was revised in October 2013, in particular for the following sections:

- Warnings and Precautions (section 5.6: Embryofetal Toxicity), Contraindications, Dosage and Administration, Overdosage
- Use in Specific Populations (section 8.1: Pregnancy, section 8.3: Nursing Mothers, section 8.6: Females and Males of Reproductive Potential) to conform to the current DPMH PLLR hybrid format.⁵

Janssen responded to the CR letter on September 22, 2014 and provided updated labeling for Doxil incorporating recommendations made by the FDA noted above as well as results of a

¹ DOP2 Consult Request Form Doxil (doxorubicin HCl liposome injection), NDA 50718/S-046 , October 28, 2014, DARRTS Reference ID 3649410

² Division Director Summary Review, NDA 50718/S-46, November 11, 2013, DARRTS Reference ID 3404902

³ Complete Response CMC Supplement, NDA 50718/S-046, November 12, 2013, DARRTS Reference ID 3405710

⁴ Division Director Summary Review, NDA 50718/S-46, November 11, 2013, DARRTS Reference ID 3404902

⁵ Division Director Summary Review, NDA 50718/S-46, November 11, 2013, DARRTS Reference ID 3404902

randomized, open-label, single dose, 2-cycle crossover bioequivalence study of Doxil in subjects with advanced or refractory solid tumors, including patients with ovarian cancer.⁶

OHOP/DOP2 consulted the Division of Pediatric and Maternal Health-Maternal Health Team (DPMH-MHT) on October 28, 2014 to provide input for appropriate labeling of the pregnancy and nursing mothers' subsections of Doxil labeling.

BACKGROUND

Doxil and Mechanism of Action

Doxil (doxorubicin HCl liposome injection) is a topoisomerase II inhibitor that is encapsulated in liposomes, which are made up of cholesterol. The mechanism of action of doxorubicin HCl is related to its ability to bind DNA and inhibit nucleic acid synthesis. Direct measurement of liposomal doxorubicin shows that 90% of the drug remains liposome-encapsulated during circulation. The encapsulated doxorubicin HCl becomes available once the liposomes are distributed to the tissue compartment; the mechanism of doxorubicin HCl release is not understood. In contrast to doxorubicin HCl, Doxil has slower plasma clearance (0.04L/h/m² for Doxil versus 24-35 L/h/m² for doxorubicin HCl) and a small volume of distribution confined to vascular fluid volume.⁷

Doxorubicin HCl and Pregnancy

Cancer is diagnosed in one out of every 1000 pregnant women. The cancers that occur most commonly in women of childbearing age include: cervical cancer, breast cancer, thyroid cancer, lymphoma and melanoma.⁸

Animal Studies

In animal reproduction studies, Doxil was embryotoxic at doses of 1 mg/kg/day in rats and was embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about 0.12 times the recommended dose of 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.⁹

Human Studies

A Pubmed search of "doxorubicin and human pregnancy" produced numerous case reports and retrospective and prospective studies. Four articles are reviewed below.

- In a case report described by Perez, *et al.*, a 22 year-old pregnant women was diagnosed with primary mediastinal large B-cell lymphoma with a large mediastinal mass at 12 weeks gestation. The patient received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone every three weeks from 13 weeks to 31 weeks of pregnancy. The patient was induced at 34-4/7 weeks

⁶ Janssen Research and Development Clinical Overview: Bioequivalence Study DOXILNAP1002 to Support TTY Manufacturing Site, RO31059 (doxorubicin HCl liposome injection), September 12, 2014

⁷ Current Janseen Doxil Labeling received September 22, 2014.

⁸ Website: <http://www.cancer.net/coping-and-emotions/sexual-and-reproductive-health/cancer-during-pregnancy>, accessed November 4, 2014.

⁹ Website: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050467s0731b1.pdf, accessed 11/4/2014

- gestation and delivered a healthy baby boy. The infant was followed to one year of age and had no physical malformations or developmental delays.¹⁰
- In a retrospective cohort, Mir, *et al.*, reviewed electronic medical records at a single medical institution between 1998 and 2008 and found 512 women between the ages of 15 to 45 who were diagnosed with sarcoma. Out of the 512 patients, nine women were diagnosed during pregnancy. In four cases, the diagnosis occurred after 34 weeks and chemotherapy was postponed until delivery at 35-37 weeks. The remaining five patients were diagnosed before the third trimester (between 25-28 weeks and were treated with chemotherapy (doxorubicin and ifosfamide). Out of the five patients, all five women experienced preterm births (ranging from 29 weeks +5 days to 36 weeks). At the time of the study report, the children of study patients ranged from eight months to five years of age and were healthy.¹¹
 - In a retrospective cohort study, Cardonick, *et al.*, completed a chart analysis of the Cancer and Pregnancy Registry at Cooper University Hospital in New Jersey and included data from July 1997 to December 2010. The goal of the study was to determine the effect of dose-dense chemotherapy (received cyclophosphamide and doxorubicin in standard doses in a different dose schedule, every two weeks, followed by either paclitaxel or docetaxel every two weeks, with a total of one to four cycle) versus conventional chemotherapy (cyclophosphamide and doxorubicin in standard doses every three weeks for a total of four cycles) during pregnancy on maternal and neonatal outcomes. Ten patients were in the dose-dense cohort and 99 patients were in the conventional chemotherapy cohort. Treatment was started after the first trimester in all patients. Briefly, the study demonstrated the following neonatal outcomes:
 - 1 congenital anomaly in dose-dense cohort: Pyloric stenosis
 - 3 congenital anomalies in the conventional cohort (Holoprosencephaly, asymptomatic main pulmonary artery fistula, hemangioma of the eye)
 - 1 neonatal death in the conventional cohort: severe autoimmune disorder (thought to be unrelated to chemotherapy exposure)

The incidence of malformations in both groups was 3.6%, which is similar to the rate of malformations in the US (2-4%). Although the study is small, there were no significant neonatal or maternal effects that occurred with more frequent dose-dense chemotherapy.¹²

- In a prospective study done by Berry, *et al.*, 24 pregnant women with primary (n=22) or recurrent breast cancer (n=2) were treated with chemotherapy (fluorouracil, doxorubicin, cyclophosphamide) given every three to four weeks after the first trimester of pregnancy for an average of four cycles during pregnancy. Treatment ranged from 11 weeks (one patient started at 11 weeks with the other women starting after the first trimester) to 33 weeks gestation. Twenty-four infants were born with gestational ages ranging from 33-38 weeks. The study demonstrated the following neonatal outcomes:

¹⁰ Perez et al. Primary Mediastinal Large B-Cell Lymphoma during Pregnancy. Case Reports in Hematology. 2012; Article ID 197347, 1-3.

¹¹ Mir, et al. Doxorubicin and ifosfamide for high-grade sarcoma during pregnancy. Cancer Chemotherapy and Pharmacology. 2011.

¹² Cardonick, et al. Maternal and Neonatal Outcomes of Dose-Dense Chemotherapy for Breast Cancer in Pregnancy. Obstetrics and Gynecology. 2012; 120 (6): 1267-1272.

- 3 preterm deliveries: 1 due to preeclampsia, 2 due to idiopathic preterm labor
- 1 infant had birth weight that was lower than the 10th percentile for gestational age
- 2 infants required oxygen for 48 hours for transient tachypnea of the newborn
- 1 infant (born at 33 weeks) was diagnosed with hyaline membrane disease resulting from prematurity
- 1 infant developed leukopenia without infectious sequelae (mother had received chemotherapy two days prior to delivery)

At the time of the study report, the children of study patients ranged from six months to eight years of age and were healthy. The authors of the study concluded that women with breast cancer can be treated with chemotherapy without exposing the fetus to harm.¹³

Reviewer Comments

The case report and cohort studies reviewed above described the use of doxorubicin in combination with other chemotherapeutic agents and their effects on the fetus. There were no studies found in literature that have been done on single agent treatment of pregnant women with doxorubicin.

Doxorubicin HCl and Lactation

The Drugs and Lactation Database (LactMed)¹⁴ was searched for available lactation data on the use of Doxil and no information was found. However, doxorubicin was searched, and one case report was found. In this case report by Egan, *et al.*, plasma and milk concentrations of doxorubicin (90mg) and cisplatin were measured after intravenous administration of these agents to a lactating woman (7 months postpartum) with ovarian cancer. The peak milk levels of doxorubicin and its metabolite (doxorubicinol) were 128 and 111 µg/L respectively and occurred at 24 hours. The highest milk: plasma concentration ratio for doxorubicin was 4.43:1 at 24 hours.¹⁵ Lactmed estimated that the infant in this case report would have received 2% of maternal weight-adjusted dosage if he had been allowed to nurse throughout the 72 hours after dosing.¹⁶ It is not known if Doxil is present in human milk, but because doxorubicin is detectable in plasma and breastmilk, breastfeeding should be avoided during maternal use of Doxil.¹⁷

Doxorubicin HCl and Fertility

Animal Studies

In animal studies, Doxil caused mild to moderate ovarian and testicular atrophy in mice after receiving a single dose of 36 mg/kg of Doxil (two times the 50 mg/m² human dose based on

¹³ Berry, et al. Management of breast cancer during pregnancy using a standardized protocol. *Journal of Clinical Oncology*, 1999; 17(3); 855-861.

¹⁴Website: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁵ Egan, et al. Doxorubicin and Cisplatin excretion into human milk. *Cancer Treat Rep*. 1985; 69: 1387-1389.

¹⁶Lactmed. Doxorubicin. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2>, accessed 11/4/2014

¹⁷ Hale, Thomas. *Medications and Mother's Milk: A Manual of Lactational Pharmacology*, 15th ed. Hale Publishing, LP. 2012: 368-396.

a mg/m² basis). Hypospermia was seen in rats after repeat doses >0.25 mg/kg/day (0.03 times the 50 mg/m² human dose based on a mg/m² basis) and decrease in spermatogenesis was seen in dogs after repeat doses of 1mg/kg/day (0.4 times the 50 mg/m² human dose based on a mg/m² basis)¹⁸

Human Studies

A Pubmed search of “Doxil and human fertility” did not produce results. However, a search of “doxorubicin and human fertility” produced nine articles. Articles that discussed animal fertility and *in vitro* studies were not reviewed. Although there were no studies looking at doxorubicin alone, there were two studies that looked at the effect of multiple chemotherapeutic agents, including doxorubicin, on fertility. The two studies are reviewed below.

Females

In a retrospective analysis of 796 breast cancer patients receiving multiple chemotherapeutic agents, which included doxorubicin, Hortobagyi, *et al.*, found that none of the women younger than 30 years had menstrual abnormalities. Amenorrhea was seen in 80% of women aged 30-39 and in 96% in women aged 40-49. Hortobagyi, *et al.*, noted that ovarian failure was permanent in most women over age 40 but reversible in 50% of women under 40 years of age.¹⁹

Males

In a multicenter prospective longitudinal study, Bujan, *et al.*, looked at the effects of lymphoma treatments (which included doxorubicin and other types of chemotherapeutic drugs) on sperm characteristics and sperm DNA. Seventy-five lymphoma patients and a control group of 257 fertile men had semen analysis and sperm DNA assessments. Semen samples were taken before the start of chemotherapy and at 3, 6, 12 and 24 months after the end of treatment. At three and six months after the end of treatment, 26% and 27% of patients respectively became azoospermic. Azoospermia decreased to 15% at 12 months post-treatment and 7% at 24 months post-treatment.²⁰

Reviewer Comments:

The two studies above are limited; the results cannot be attributed to doxorubicin since multiple chemotherapeutic agents were used.

DISCUSSION

Doxorubicin HCl and Pregnancy

DPMH agrees with the current pregnancy category D classification for Doxil.²¹ Although adequate and well controlled studies have not been conducted in pregnant women, as discussed above, the likelihood of adverse fetal and infant effects is high based on the drug's

¹⁸ [Drugs@FDAhttp://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050718s0451bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050718s0451bl.pdf); accessed 11/5/2014.

¹⁹ Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. NCI Monogr 1986;1:105–109

²⁰ Bujan, et al. Impact of lymphoma treatments on spermatogenesis and sperm deoxyribonucleic acid: a multicenter prospective study from CECOS network. Fertility and Sterility. 2014; 102 (3): 689.

²¹ Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

mechanism of action and adverse fetal and infant outcomes observed in animal models and animal reproduction studies, which have shown that doxorubicin HCl is embryotoxic in rats and abortifacient in rabbits. Therefore, a pregnancy category D appropriately characterizes the risk with maternal use of Doxil.

Doxorubicin HCl and Lactation

Overall, DPMH agrees with the sponsor's proposed nursing mothers regulatory statement²² in the "Nursing Mothers" section of labeling with minor changes as listed below. The following is DPMH's proposed language:

It is not known whether Doxil is present in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue nursing during treatment with DOXIL.

Reviewer Comments:

- *The statement DPMH is proposing, "Because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue nursing during treatment." is a truncated version of the regulatory statement from the proposed PLLR when there is concern that a drug may be harmful to a lactating infant. Therefore, it is recommended that nursing be discontinued during treatment with Doxil.*
- *The word (b)(4) was changed to "present," which is underlined above, and is the approved word used per the proposed PLLR. Drugs can enter into breast milk in different ways (excretion, diffusion, active transport, etc). Therefore, when we do not know that exact mechanism by which a drug enters into breast milk, the correct term is "present."*

Doxorubicin HCl and Contraception

Overall, DPMH agrees with the sponsor's proposed "Females and Males of Reproductive Potential" section of labeling with minor changes as listed below. The following is DPMH's proposed language for *Contraception: Females*. The other sections of "Females and Males of Reproductive Potential" were not changed.

DOXIL can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during (b)(4)

Reviewer Comments

- *The term (b)(4) contraception was changed to "effective" contraception. (b)(4) DPMH recommends removing the term (b)(4)*

²² Refer to 201.57(c)(9)(iii)(B) and (C) for the use of the appropriate nursing mothers regulatory statement.

Doxorubicin HCl and Infertility

Animal studies done in mice, rats and dogs have shown ovarian and testicular atrophy, hypospermia, and decreased spermatogenesis respectively. However, there are no human studies that have looked at the effect of doxorubicin HCl or Doxil alone (not in combination with other chemotherapeutic agents) on human fertility. The study by Bugan, *et al.*, reviewed above evaluated doxorubicin in combination with other chemotherapeutic agents and their effect on male fertility; in this study, 7% of men treated with doxorubicin and other chemotherapeutic agents remained azoospermic two years after treatment. In the study by Hortobagyi, *et al.*, women treated with doxorubicin and other chemotherapeutic agents, amenorrhea was commonly seen in women over the age of 30 and was permanent in women over 40 years of age.

Currently, oncology standard of care has several options for fertility preservation in both males and females. For males who have reached puberty, freezing sperm at diagnosis is the gold standard for fertility preservation when treating men who have cancer. For females, options for fertility preservation include oocyte and embryo freezing and ovarian tissue preservation (for prepubertal girls when embryo freezing or oocyte, which requires ovarian stimulation, is not appropriate). There is currently insufficient evidence regarding the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogs) as a fertility preservation method.²³

Reviewer Comments

Based on animal data and human studies, DPMH agrees with the sponsor's proposed language in section (b) (4) "Females and Males of Reproductive Potential: Infertility."²⁴ Since information about potential infertility with chemotherapeutic agents and options for fertility preservation are currently part of oncology standard of care, it is sufficient to have infertility information only in section (b) (4) of labeling. (b) (4)

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. (b) (4)

²³ Loren et al. Fertility Preservation for Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 2013: 1-12.

²⁴ See Appendix A for Sponsor's proposed Doxil Labeling

(b) (4) The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on (b) (4) contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

CONCLUSIONS AND RECOMMENDATIONS

DPMH-MHT has the following recommendations for Doxil labeling. See attached label for details.

- **Warnings and Precautions, Section 5.6**
 - Minor revisions were made to the “Embryofetal Toxicity” subsection of Doxil labeling in order to include specific information about when to use contraception and for what length of time.
- **Pregnancy, Section 8.1**
 - Pregnancy category D classification is appropriate for Doxil.
 - The pregnancy subsection of Doxil labeling was structured in the spirit of the proposed PLLR, while complying with the current pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(i)).
- **Nursing Mothers, Section 8.3**
 - Minor revisions were made to the “Nursing Mothers” subsection of Doxil labeling for consistency with language in the proposed PLLR, while complying with the current nursing mothers pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(ii)(C)).
 - DPMH-MHT agrees that breastfeeding is not recommended with maternal use of Doxil.
- **Females and Males of Reproductive Potential, Section (b) (4)**
 - Minor revisions were made to the “Females and Males of Reproductive Potential” subsection of Doxil labeling in order to make this section of labeling consistent with other drugs that require effective contraception.
 - Since information about potential infertility with chemotherapeutic agents and options for fertility preservation are currently part of oncology standard of care, it is sufficient to have infertility information only in section (b) (4) of labeling. (b) (4)

DPMH-MHT DOXIL LABELING

DPMH-MHT recommends the following revision to Pregnancy and Nursing Mothers sections of Doxil labeling. These recommendations were discussed at a labeling meeting on November 17, 2014. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (See Appendix A for the applicant's proposed pregnancy and nursing mothers' labeling)

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- Embryofetal Toxicity: [REDACTED] (b) (4)
[REDACTED] (5.6)

-----USE IN SPECIFIC POPULATIONS-----

[REDACTED] (b) (4)

Warnings and Precautions

5.6 Embryofetal Toxicity

DOXIL can cause fetal harm when administered to a pregnant woman. At doses approximately 0.12 times the recommended clinical dose, DOXIL was embryotoxic and abortifacient in rabbits. [REDACTED] (b) (4)

[REDACTED] (b) (4)
[REDACTED] [see Use in Specific Populations (8.1) and (b) (4)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

DOXIL can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, DOXIL was embryotoxic in rats and abortifacient in rabbits following its intravenous administration during organogenesis at doses approximately 0.12 times the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Data

Animal data

DOXIL was embryotoxic at doses of 1 mg/kg/day in rats and was embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about 0.12 times the recommended dose of 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.3 Nursing Mothers

It is not known whether DOXIL is present in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue nursing during treatment with DOXIL.

^(b) ⁽⁴⁾ Females and Males of Reproductive Potential

Contraception

Females

DOXIL can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during ^{(b) (4)}

Males

DOXIL may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and for 6 months after treatment with DOXIL [see *Nonclinical Toxicology (13.1)*].

Infertility

Females

In females of reproductive potential, DOXIL may cause infertility and result in amenorrhea ^{(b) (4)}. Premature menopause can occur with doxorubicin HCl. Recovery of menses and ovulation is related to age at treatment.

Males

DOXIL may result in oligospermia, azoospermia, and permanent loss of fertility. Sperm counts have been reported to return to normal levels in some men. This may occur several years after the end of therapy [see *Nonclinical Toxicology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity

^{(b) (4)}

Infertility

Advise females and males of reproductive potential that DOXIL may cause temporary or permanent infertility [see *Use in Specific Populations* ^{(b) (4)}].

Nursing Mothers

Advise ^{(b) (4)} not to breastfeed during treatment with DOXIL [see *Use in Specific Populations (8.3)*].

APPENDIX A – Applicant’s Proposed Pregnancy and Nursing Mothers Labeling

(b) (4)



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/s/

MIRIAM C DINATALE
11/20/2014

LYNNE P YAO
11/24/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 4, 2014
Requesting Office or Division: Office on Oncology Products 2 (DOP2)
Application Type and Number: NDA 050718/S-046
Product Name and Strength: Doxil (doxorubicin HCl liposome injection)
20 mg/10 mL (2mg/mL) and 50 mg/25 mL (2 mg/mL)
Submission Date: September 22, 2014
Applicant/Sponsor Name: Janssen Products, LLP
OSE RCM #: 2014-2032
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

As a part of this S-046 resubmission, DOP2 requested that we review the revised Doxil container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective.

1.1 REGULATORY HISTORY

On July 12, 2013, Janssen Research and Development, LLC on behalf of Janssen Products LLP submitted a CMC Supplement (S-046) for the addition of another facility, TTY Biopharm located in Taiwan, for the manufacture of Doxil as well as other manufacturing changes.

On November 12, 2013, the Agency sent Janssen a Complete Response because the supplement lacked a bioequivalence study, and due to other concerns.

On September 22, 2014, Janssen responded to the Complete Response. Janssen addressed the question and comments posed by the Agency regarding the bioequivalence study; chemistry, manufacturing & controls; and labeling in this S-046 resubmission.

DMEPA previously reviewed the proposed Doxil container labels and carton labeling for S-46 and made recommendations.¹

2 DISCUSSION

Janssen's revised container labels and carton labeling incorporated all of our recommendations except regarding the statement (b) (4). In our previous review we recommended the statement, (b) (4) be changed to read "Single- (b) (4) Vial. Discard unused portion." Janssen does not agree with the use of the statement "single- (b) (4) and would like to retain the statement, "single use". DMEPA finds the statement okay at this time. Therefore, we have no further comments.

3 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective.

¹ Townsend, O. Label and Labeling Review for Doxil (doxorubicin HCl liposome) (NDA 050718). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 SEP 13. 9 p. OSE RCM No.: 2013-1713.

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/s/

OTTO L TOWNSEND
11/04/2014

CHI-MING TU
11/05/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 1, 2013

To: Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 50718/S-046
Doxil[®] (doxorubicin HCl liposome injection)
OPDP Review of Carton/Container Labeling

Background

This consult is in response to DOP2's October 29, 2013, request for OPDP's review on carton and container labeling for Doxil[®] (doxorubicin HCl liposome injection) (Doxil).

Doxil 20mg Carton/Container Labeling

(b) (4)



Doxil 50mg Carton/Container Labeling

(b) (4)



Consult Response:

The Doxil 20mg and 50mg carton/container labeling present the claim,

(b) (4)



OPDP recommends deleting the above claim.

Thank you for the opportunity to comment on the proposed carton and container labeling for Doxil. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185 or Quynh-Van.Tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
11/01/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 13, 2013

Reviewer(s): Otto L. Townsend, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Doxil (Doxorubicin HCl Liposome Injection)
20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL)

Application Type/Number: NDA 050718/S-046

Applicant: Janssen Products, LP

OSE RCM #: 2013-1713

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review is written in response to a consult request received from the Division of Oncology Products 2 (DOP2). On July 12, 2013, the Applicant submitted a Chemistry, Manufacturing and Controls (CMC), prior approval supplement providing for an additional manufacturing facility. On August 12, 2013, DOP2 requested the Division of Medication Error Prevention and Analysis (DMEPA) assess the proposed container labels, carton and insert labeling for Doxil Injection (NDA 050718) submitted with the CMC supplement.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 12, 2013, submission.

- Active Ingredient: Doxorubicin HCl Liposome Injection
- Indication of Use: Treatment of Ovarian Cancer, AIDS-Related Kaposi's Sarcoma and Multiple Myeloma.
- Route of Administration: Intravenous Infusion
- Dosage Form: Injection
- Strength: 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL)
- Dose and Frequency:
 - Ovarian Cancer: 50 mg/m² every four weeks.
 - Patients with AIDS-Related Kaposi's Sarcoma: 20 mg/m² every three weeks.
 - Multiple Myeloma: In combination with Bortezomib. Bortezomib 1.3 mg/m² intravenous bolus on days 1, 4, 8 and 11 every three weeks. Doxil 30 mg/m² as a one hour infusion on day 4 following Bortezomib.
- How Supplied:
 - SINGLE- (b) (4) VIALS:
 - 10 mL vial containing doxorubicin HCl at a concentration of 2 mg/mL
 - 25 mL vial containing doxorubicin HCl at a concentration of 2 mg/mL
- Storage: Store refrigerated at 2° to 8°C (36° to 46°F). (b) (4)
- Container and Closure System: Available in individually cartoned glass vials.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Doxil medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the container labels, carton and insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	March 16, 2013 (date of last DMEPA review – OSE review #2013-678) to August 19, 2013
Drug Names	Active Ingredient: Doxorubicin Product Name: Doxorubicin Verbatim Term: Doxorub*, Adriam*, Doxil*
MedDRA Search Strategy	Medication Errors HLT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 14 cases. None of these cases were relevant to this review because they were from clinical trials and did not describe a medication error involving Doxil.

2.2 LITERATURE SEARCH

We searched PubMed with the search terms “Doxorubicin medication errors” and “Doxil medication errors”. Additionally, we searched The Institute for Safe Medication Practices (ISMP) publications on August 23, 2013 for additional cases and actions concerning Doxil using the search term, “doxorubicin”.

There was one article from the PubMed search that discussed findings from a survey of practitioners’ experiences with oncology drug shortages and their impact on cancer care.¹ The authors concluded that such shortages could lead to increased risk of medication errors, but specific cases were not included.

The ISMP Medication Safety Alert discussed the importance of reviewing clinical information systems and other computer databases to ensure the recently approved generic Doxorubicin Liposomal product is clearly designated as a liposomal product.²

Although both are important, neither issue is relevant to this Doxil review.

¹ McBride A, Holle LM, Westendorf C, et al. National survey on the effect of oncology drugs shortages on cancer care. *Am J Health-Syst Pharm.* 2013;70:609-17.

² Institute for Safe Medication Practices. Safety Briefs: Check computer listing for generic DOXOrubicin liposome injection. ISMP Med Saf Alert Acute Care 2013 May 2; 18(9): 1-2.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with post marketing medication error data, DMEPA evaluated the following:

- Container Labels submitted July 12, 2013 (Appendix B)
- Carton Labeling submitted July 12, 2013 (Appendix C)
- Insert Labeling submitted July 12, 2013.

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had not completed any reviews of this product since its initial approval November 17, 1995.

3 CONCLUSIONS

DMEPA recommends the following recommendations be implemented prior to approval of this supplement. If you have questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

3.1 COMMENTS TO THE APPLICANT

A. Container Labels and Carton Labeling

1. Revise the total drug content and strength per milliliter statement to appear in a stacked format, similar to:

20 mg in 10 mL
(2 mg/mL)

2. Change statement, [REDACTED]^{(b) (4)} to read “Single- [REDACTED]^{(b) (4)} Vial. Discard unused portion.”

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

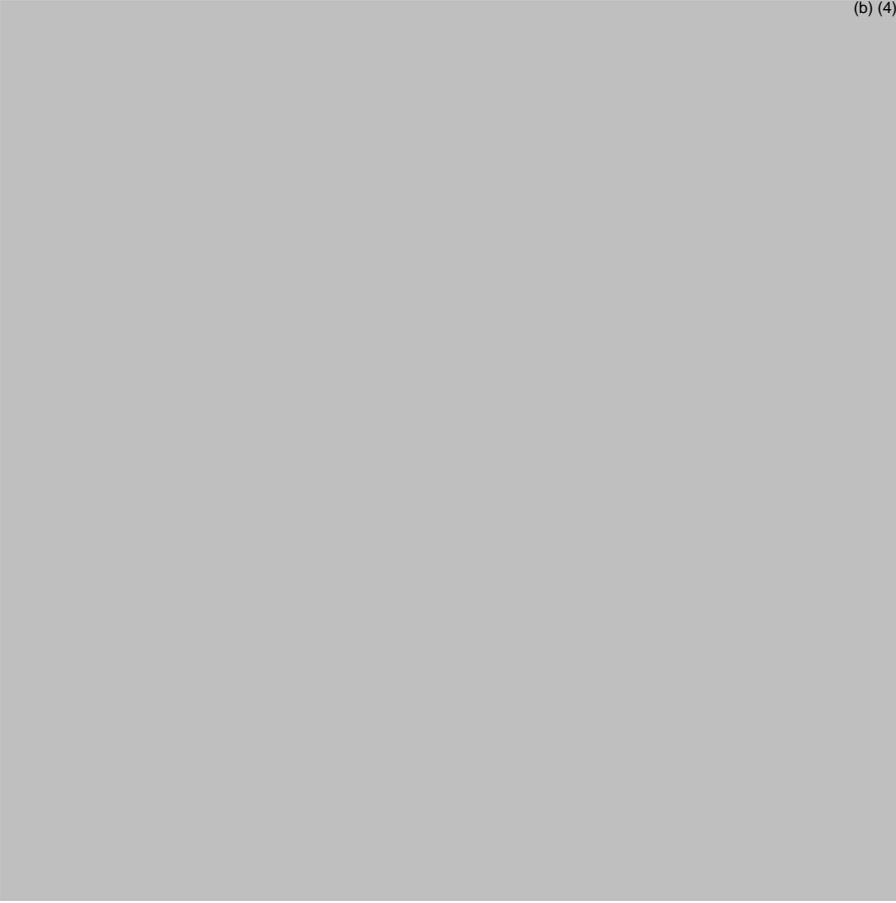
The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012 and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix B: Container Labels

(b) (4)



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OTTO L TOWNSEND
09/13/2013

TODD D BRIDGES
09/13/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-46

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Initial Planning Meeting Minutes
October 16, 2014

Product: DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion

sNDA: 50718/S-046
(Complete Response-CMC Prior Approval Supplement with Manufacturing Changes)

eCTD submission: SDN 926

Submission Date: September 22, 2014
Received Date: September 22, 2014
Sponsor: Janssen Research & Development, LLC

Purpose: The purpose of this resubmission is to provide Janssen's response to the Agency's Complete Response letter dated November 12, 2013.

This submission is composed of the following:

- Clinical, Biopharmaceutics, and Clinical Pharmacology Overview of Bioequivalence Study DOXILNAP1002 (based on the outcome of the 14 April 2014 meeting)
- Responses to questions and comments in response to November 12, 2013 letter regarding CM&C
- Responses to questions and comments in response to November 12, 2013 letter regarding general labeling comments provided in the package insert. In addition the following changes were made:
 - Removal of "liver impairment" from the header in the Boxed Warning section;
 - Revision to the order of term as in Section 17, Patient Counseling information
- Draft Carton Container Labeling 20 mg vial, 20 mg carton, 50 mg vial, and 50 mg carton
- Data collected to show the interchangeability between the [REDACTED] (b) (4) [REDACTED] of drug product manufactured at TTY. Additionally, CM&C updates to the dossier are detailed in the Introduction (Module 2.2), along with a resubmission of Drug Product (Module 3.2.P).

Currently Marketed Indications:

- **Ovarian cancer**
After failure of platinum-based chemotherapy.
- **AIDS-related Kaposi's**
After failure of prior systemic chemotherapy or intolerance to such therapy.
- **Multiple Myeloma**
In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

Current Review Team for complete response of sNDA 50718/S-046
(* denotes meeting attendees)

*Patricia Keegan, M.D., Director, DOP2
Monica Hughes, M.S., CPMS, DOP2
Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager
*Marc Theoret, M.D., Clinical Team Leader (CDTL)
*Meredith Chuk, M.D., Medical Officer (DOP 2)
*Whitney Helms, Ph.D., Non-Clinical (TL)
Shawna Weis, Ph. D, Non-Clinical

Complete Response Resubmission

sNDA 50718/S-046 DOXIL (doxorubicin HCl liposome injection) for intravenous infusion

Gene Williams, Ph.D., Clinical Pharmacology (TL)

*Safaa Burns, Clinical Pharmacology Reviewer

Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader, ONDQA

*Okpo Eradiri, Ph. D., Biopharmaceutics Reviewer

Hasmukh Patel, Ph.D., Acting Branch Chief

*Kavita Vyas, CMC Reviewer

Teicher Agosto, ONDQA RPM

Robert Wittorf, OC, OMPQ

Frances Fahnbulleh, OSE, Safety RPM

Christine Bina, OC, Drug Shortage

Carole Broadnax, OPDP

*Otto Townshend, DMEPA Reviewer

Chi-Ming (Alice) Tu, DMEPA TL

Ann Marie Trentacosti, SEALD Review

*Carrie Bitman, Panorama Liaison

Regulatory Background:

<p>CMC PAS Supplement 046 with request for BE waiver and nonclinical data was submitted July 12, 2013</p>	<p>Complete Response (CR) Letter and labeling comments to PI Issued November 12, 2013</p>	<p>This supplemental application, submitted as PAS provided for:</p> <ul style="list-style-type: none">• a new manufacturing site, TTY Biopharm, located in Chungli, Taoyuan, Taiwan, R.O.C. for the (b) (4) and (b) (4) product;• a change in batch size of the drug product to (b) (4)• a new (b) (4) stopper for the drug product;• addition of a secondary packaging site at (b) (4) and,• a request for waiver from the requirement to support the proposed manufacturing changes• by conducting a bioequivalence (BE) study; the waiver is supported by the results of a• nonclinical bioequivalence assessment.
<p>DOP 2, ONDQA Teleconference with Janssen</p>	<p>Teleconference held April 14, 2014; Meeting Minutes issued May 14, 2014</p>	<p>Discussion regarding the results of the Incurred Sample reanalysis (ISR) for free</p>

**Complete Response Resubmission
sNDA 50718/S-046 DOXIL (doxorubicin HCl liposome injection) for intravenous infusion**

		doxorubicin in the ongoing multi-center BE study DOXILNAP1002
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*A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Discussion Items:

1. Review Status: 4 Months (Action Date: January 22, 2015)

- Confirmed the signatory for this complete response: Dr. Keegan, DOP 2
- Noted that the clinical development of doxorubicin HCl liposome injection for intravenous infusion has been conducted under IND 036778
- Noted that the IRB Waiver of BE Study DOXILNAP1002 granted under IND 036778 on June 23, 2013.
- Noted that on April 14, 2014, DOP 2, ONDQA, and Janssen held a teleconference to discuss the results of the Incurred Sample reanalysis (ISR) for free doxorubicin in the ongoing multi-center BE study DOXILNAP1002 entitled, entitled "A Pivotal Bioequivalence Study of DOXIL/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies Including Subjects with Ovarian Cancer, in support of a proposed new manufacturing facility for DOXIL," conducted under IND 036778.
- The review team discussed the submission and agreed that it was a complete submission in response to the Complete Response letter.
- Janssen submitted a minor amendment regarding the individual unit in-vitro release data that was included within the "Complete Response" document in Module 1.2. Per email from BE reviewer dated October 2, 2014, this submission was considered a minor amendment

2. Consults Submitted:

Discussion During Meeting:

The review team discussed the following consults:

- OSE /DMEPA- Carton Container
- CMC/Manufacturing site Inspections (EES)- Under the original application (Supplement 046) that was submitted July 2013 an inspection was completed at TTY on 9/27/13 and no 483 was issued. OPQ stated that an inspection is not needed however they will be submitting a consult via Panorama to verify.
- Microbiology - will be submitted via OPQ through Panorama
- OPDP
- Maternal and Child Health- a consult was submitted for review of labeling revisions

Post Meeting follow up with OPQ: RPM followed up via email with OPQ review team as to whether request for categorical exclusion should be included with the complete response submission. In an email received from DS Reviewer/ TL on October 17, 2014, because this resubmission is in response to items not related to

Complete Response Resubmission

sNDA 50718/S-046 DOXIL (doxorubicin HCl liposome injection) for intravenous infusion

additional manufacturing scale. The previously submitted environmental assessment (EA) is applicable to the current submission.

3. Upcoming/TBD Internal Team Meetings:

- a. **Filing Meeting:** None
- b. **Labeling Meetings:** 2 scheduled

Discussion During Meeting: During the planning meeting the team proposed holding two labeling meetings. For the first labeling meeting, nonclinical and maternal health sections will go first followed by clinical pharmacology and then clinical if time permits. For the second labeling meeting clinical pharmacology sections not covered during the first labeling meeting will be discussed first followed by CMC and DMEPA discussion of the labeling and carton and container. Clinical agreed to review labeling separately.

4. Miscellaneous Items or Issues:

Discussion During Meeting: Panorama IT representative attended the meeting to provide a short demo on using Panorama as this CMC supplement will be managed entirely under Panorama.

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/s/

ANUJA PATEL
01/21/2015

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, January 14, 2015 2:51 PM
To: 'Scurato, Matthew [JRDUS]'
Subject: FDA Tcon- Friday, January 16, 2015- NDA 50718/ Supplement 46 (Complete Response)

Dear Mr. Scurato,

We refer to the phone between yourself and I at approximately 2:45 PM, EST today. We also refer to teleconference held today, January 14, 2015 from 10:30 AM to 11:30 AM, EST between FDA and Janssen to discuss your counterproposal received January 9, 2015 in response to our December 31, 2014 Preliminary Comments. During the teleconference we agreed to hold a second teleconference to complete our discussion.

We propose holding a 1 hour teleconference on Friday, January 16, 2015 at 9:00 AM, EST. Kindly confirm the proposed date and time and provide a dial in number.

In addition, we have the following comment from Division of Pediatric and Maternal Health regarding **Section 8.2 Lactation**:

[Section 8.2 Lactation in the package insert \(PI\) needs to be corrected.](#)

[Currently Section 8.2 looks like this:](#)



[This section should look like this:](#)

8.2 Lactation

Risk Summary

It is not known whether Doxil is present in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue breastfeeding during treatment with DOXIL.

Please do not submit revised labeling at this time as we will incorporate the above comment into the labeling for discussion on Friday, January 16, 2015. During the teleconference on Friday we will outline the next steps.

Kindly acknowledge receipt of this email.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
01/15/2015

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, January 06, 2015 4:54 PM
To: 'Scurato, Matthew [JRDUS]'
Cc: Griffin, Norma
Subject: FDA Comment Regarding Carton/Container: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits

Importance: High

Dear Mr. Scurato,

Thank you for your voice message and your email below sent January 14, 2014. I apologize for the delay in my response as I am having email issues today.

We have the following response for Question 1 below that was sent to FDA via email on January 5, 2015:

1. **On the 31 December memorandum it states “General comment regarding 20 and 50 mg carton and container label Janssen submitted (see below)”. We do not see any comments regarding these. The labels appear to be the ones we submitted with no changes. Could you please clarify.**

FDA response: We have the following comment regarding both 20 and 50 mg carton and container label that was inadvertently left from the Memorandum that was emailed to you on December 31, 2014.

- **Replace (b) (4) with “Liposomal Formulation- Do not substitute for Doxorubicin HCl”**

I am working on Question 2 and will follow up you soon.

Anuja

From: Scurato, Matthew [JRDUS] [mailto:MSCURATO@ITS.JNJ.COM]
Sent: Monday, January 05, 2015 10:54 AM
To: Patel, Anuja
Cc: Griffin, Norma
Subject: RE: Request for Response- Updated Teleconference Date/Time: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits
Importance: High

Hi Ms. Patel

I am checking on availability for January 14th. In the meantime I have two questions:

1. On the 31 December memorandum it states “General comment regarding 20 and 50 mg carton and container label Janssen submitted (see below)”. We do not see any comments regarding these. The labels appear to be the ones we submitted with no changes. Could you please clarify.
2. Do you have the FDA comments with track changes for the package insert as a WORD document? If so could you send that to me in an email?

Regards
Matt Scurato



Janssen Research & Development, LLC
920 Route 202, P.O. Box 300
Raritan, NJ 08869
Phone: 908 704 5187

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From: Scurato, Matthew [JRDUS] [<mailto:MSCURATO@ITS.JNJ.COM>]
Sent: Thursday, January 01, 2015 10:21 AM
To: Griffin, Norma
Cc: Patel, Anuja
Subject: RE: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits

Good Morning Norma,

I am confirming receipt of the email and attached documents

Regards
Matt Scurato



Janssen Research & Development, LLC
920 Route 202, P.O. Box 300
Raritan, NJ 08869
Phone: 908 704 5187

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From: Griffin, Norma [<mailto:Norma.Griffin@fda.hhs.gov>]
Sent: Wednesday, December 31, 2014 3:49 PM
To: Scurato, Matthew [JRDUS]
Cc: Patel, Anuja
Subject: RE: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits
Importance: High

Good Afternoon Matthew,

On behalf of Anuja Patel, your RPM for this application, I am sending you 'FDA Proposed Labeling Edits' for this NDA submission (NDA 50718/Supp 046 (Complete Response)). Attached is a memorandum and the package insert in 2 versions (Tracked Changes PDF and CLEAN WORD version). The WORD version is a CLEAN document (no tracked changes) that includes those edits (by Janssen and FDA) that were accepted by FDA. Refer to the PDF tracked changes document as reference. We ask that you provide your response to Anuja by Friday, January 9, 2015.

Kindly respond to confirm receipt of this email and the attached documents.

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Telephone 301.796.4255

From: Griffin, Norma
Sent: Wednesday, December 31, 2014 10:32 AM
To: 'mscurato@its.jnj.com'
Subject: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits
Importance: High

Good Morning Matthew,

Anuja Patel, your RPM for this application is out of the office. I am currently working on final edits from the Review Team and will be sending you 'FDA Proposed Labeling Edits' today. I just wanted you to know that they will be forthcoming.

In addition, I believe that Anuja had scheduled a TCON with you for JAN 8th, 2015, to discuss the labeling. Given the timing of getting these edits to you, Anuja will most likely re-schedule the TCON. I will let Anuja update you on that aspect.

I will email you again shortly.

Regards,

Norma S. Griffin
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Norma.Griffin@fda.hhs.gov
Telephone 301.796.4255

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/s/

ANUJA PATEL
01/06/2015

Griffin, Norma

From: Griffin, Norma
Sent: Wednesday, December 31, 2014 3:49 PM
To: 'mscurato@its.jnj.com'
Cc: Patel, Anuja
Subject: RE: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits

Importance: High



NDA 50718/Supp 046
Resubmission (1...



FDA 12312014
Proposed Edits ...



FDA 12312014
Proposed Edits ...

Good Afternoon Matthew,

On behalf of Anuja Patel, your RPM for this application, I am sending you 'FDA Proposed Labeling Edits' for this NDA submission (NDA 50718/Supp 046 (Complete Response)). Attached is a memorandum and the package insert in 2 versions (Tracked Changes PDF and CLEAN WORD version). The WORD version is a CLEAN document (no tracked changes) that includes those edits (by Janssen and FDA) that were accepted by FDA. Refer to the PDF tracked changes document as reference. We ask that you provide your response to Anuja by Friday, January 9, 2015.

Kindly respond to confirm receipt of this email and the attached documents.

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Telephone 301.796.4255

From: Griffin, Norma
Sent: Wednesday, December 31, 2014 10:32 AM
To: 'mscurato@its.jnj.com'
Subject: NDA 50718/Supp 046 (Complete Response)/ Janssen - FDA Proposed Labeling Edits
Importance: High

Good Morning Matthew,

Anuja Patel, your RPM for this application is out of the office. I am currently working on final edits from the Review Team and will be sending you 'FDA Proposed Labeling Edits' today. I just wanted you to know that they will be forthcoming.

In addition, I believe that Anuja had scheduled a TCON with you for JAN 8th, 2015, to discuss the labeling. Given the timing of getting these edits to you, Anuja will most likely re-schedule the TCON. I will let Anuja update you on that aspect.

I will email you again shortly.
Regards,

Norma S. Griffin

*Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research*

*Email: Norma.Griffin@fda.hhs.gov
Telephone 301.796.4255*



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 31, 2014

From: Norma Griffin on behalf of
Anuja Patel, M.P. H., Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 50718/S-046 Resubmission of Complete Response –
FDA Proposed Comments to Janssen Package Insert and Carton/Container
Submission received

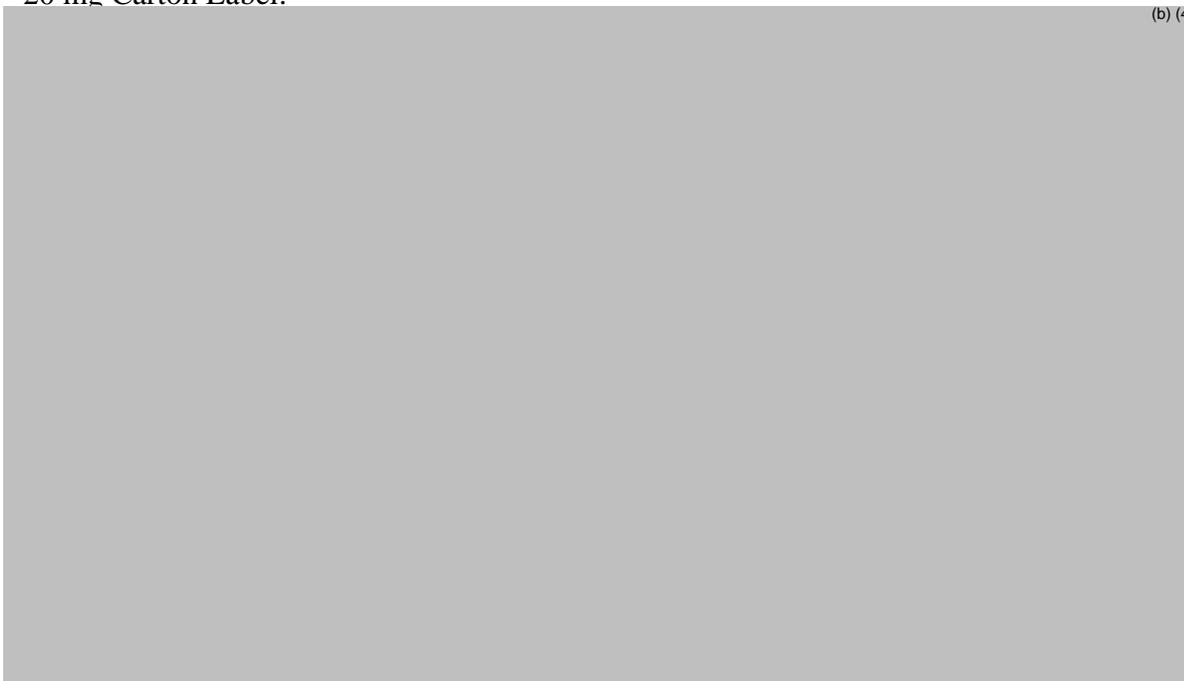
Please find attached FDA's counter-proposal and requests for clarification to your package insert and carton and container labeling as submitted and received on September 22, 2014, in response to our November 12, 2013, complete response letter.

Please provide a response to FDA's proposed changes by January 9, 2015. In addition to formally submitting your response to the NDA, please email me a copy of your responses to our comments and questions below as well as the revised carton and container labeling.

Please note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in Office of Prescription Drug Promotion (OPDP) and additional comments may follow.

General Comment Regarding 20 mg and 50 mg Carton and 20 mg and 50 mg Container Labels Janssen Submitted (see below):

20 mg Carton Label:



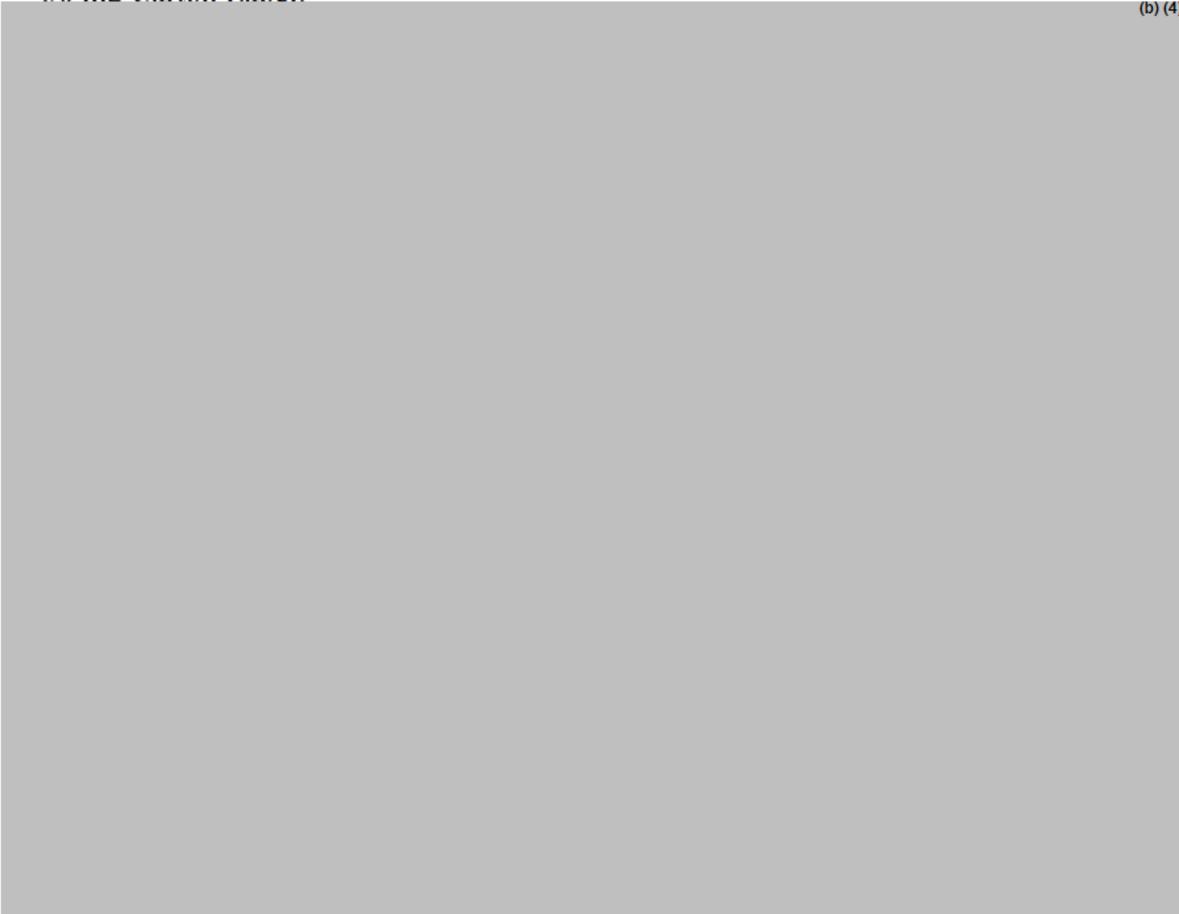
20 mg Container Label:

(b) (4)



50 mg Carton Label:

(b) (4)



50 mg Container label:



Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachments:

- FDA 12.31.2014 Proposed Edits to Sponsor – Package Insert Tracked Changes PDF version
- FDA 12.31.2014 Proposed Edits to Sponsor CLEAN – Package Insert WORD version

79 page(s) has been Withheld in Full as draft labeling (CCI/TS)
immediately following this page

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/s/

NORMA S GRIFFIN
12/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION		
TO: CDER Pediatric and Maternal Health Staff <i>(please check)</i> Pediatrics <input type="checkbox"/> Maternal Health <input checked="" type="checkbox"/> Both <input type="checkbox"/>		FROM <i>(Name, Office/Division, and Phone Number of Requestor)</i> : Anuja Patel, Division of Oncology Products 2, 301 796 9022		
DATE 10.28.14	IND NO.	NDA/BLA NO. sNDA 50718 Supp 046 (Complete Response)	TYPE OF DOCUMENT sNDA/ PAS	DATE OF DOCUMENT 9.22.14
NAME OF DRUG Doxil (doxorubicin HCl liposome injection)		NAME OF FIRM Janssen	CLASSIFICATION OF DRUG Anthracycline antibiotic	PDUFA Goal Date January 22, 2015
Requested Consult Completion Date: Due November 21, 2014		<input type="checkbox"/> Urgent* (< 14 days)	<input checked="" type="checkbox"/> Priority (14-29 days)	<input type="checkbox"/> Routine \geq 30 days
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.				
REASON FOR REQUEST				
Pediatrics: <input type="checkbox"/> Labeling Review <input type="checkbox"/> Written Request/PPSR <input type="checkbox"/> PREA PMR/General Regulatory Question <input type="checkbox"/> SPA <input type="checkbox"/> Action Letter Review <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Other Protocol Review <input type="checkbox"/> Meeting Attendance <input type="checkbox"/> PeRC Preparation Assistance <input type="checkbox"/> Other (please explain):		Maternal Health Team: <input checked="" type="checkbox"/> Labeling Review <input type="checkbox"/> Pregnancy Exposure Registry (protocol or report) <input type="checkbox"/> Clinical Lactation Study (protocol or report) <input type="checkbox"/> Pregnancy PK (protocol or report) <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Risk Management – Pregnancy Prevention and Planning <input type="checkbox"/> Evaluation of possible safety signal <input type="checkbox"/> Guidance development <input type="checkbox"/> Other (please explain):		
Link to electronic submission (if available): EDR Location: SDN 926 \\CDSESUB1\evsprod\NDA050718\050718.enx		Materials to be reviewed: Package Insert		
1. Please briefly describe the submission including drug's indication(s): This is Janssen's resubmission of the PAS Complete Response, for NDA 50718/Supplement 046 (in response to the November 12, 2013 Complete Response letter). Janssen submitted proposed labeling changes to PI in response to our November 12, 2013 letter. In addition, Janssen submitted revised labeling for their 20 mg and 50 mg carton, and 20 mg and 50 mg container. Lastly, revisions are made to patient counseling section as well.				
2. Describe in detail the reason for your consult. Include specific questions: Are there any suggested changes to review relevant sections of label that is undergoing extensive revision for current PLR format. DOP 2 requests review of sections 8.1 and 8.3 of the package insert				
3. Meeting dates: Labeling Meetings: November 17, 2014 and November 19, 2014				
4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years): N/A				
Review team: Project Manager: Anuja Patel Clinical reviewer & Team Leader: Meredith Chuk/ Marc Theoret				

Pharmacology/Toxicology reviewer & Team Leader: Shawna Weis/Whitney Helms

Clinical Pharmacology reviewer & Team Leader: Safaa Burns/Gene Williams

Other: Division of Oncology Products 2 Director: Patricia Keegan

PRINTED NAME or SIGNATURE OF REQUESTOR:

Anuja Patel, RPM

METHOD OF DELIVERY (Please check)

DARRTS EMAIL HAND OTHER

Version: DARRTS 10/14/2014

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/s/

ANUJA PATEL
10/28/2014

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Anuja Patel/RPM, OHOP/DOP 2/301-796-9022

REQUEST DATE
10.27.14

IND NO.

NDA/BLA NO.
NDA 50718/S-
046

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG
Doxil (doxorubicin HCl liposome
injection)

PRIORITY CONSIDERATION
CMC Supplement
Resubmission/PAS with
Manufacturing (4 months)

CLASSIFICATION OF DRUG
Anthracycline antibiotic

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
November 24, 2014

NAME OF FIRM:
Janssen

PDUFA Date: January 22, 2015

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

EDR Location: SDN 926 <\\CDSESUB1\evsprod\NDA050718\050718.enx>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: November 17, 2014 and November 19, 2014

SIGNATURE OF REQUESTER
Anuja Patel

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check all that apply)

- eMAIL
- DARRTS
- HAND

06/18/2013

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/s/

ANUJA PATEL
10/27/2014

Labeling Meeting scheduled November 19, 2014

SIGNATURE OF REQUESTER Anuja Patel	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ANUJA PATEL
10/27/2014



NDA 50718/S-046

COMPLETE RESPONSE –CMC

Janssen Products, L.P.
Attention: Matthew Scurato
Associate Director, Global Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Scurato:

Please refer to your Supplemental New Drug Application (sNDA) dated July 12, 2013, received July 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Doxil (doxorubicin HCl liposome injection),” 20 mg/10 mL and 50 mg/25 mL.

We also refer to your September 22, 2014, resubmission, received September 22, 2014, to your supplemental new drug.

This resubmission constitutes a complete response to our November 12, 2013, action letter. The user fee goal date is January 22, 2015.

If you have any questions, please call me, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NORMA S GRIFFIN
10/08/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 30, 2014
From: Anuja Patel, DOP2/OHOP/CDER
Subject: FDA Request for Information
Janssen Products, L.P.
Attn: Matthew Scurato
Re: NDA 50718/Supplement 046 received September 22, 2014

Janssen Products, L.P.
Attention: Matthew Scurato
Associate Director, Global Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08807-0914

Dear Mr. Scurato:

Please refer to your Supplemental New Drug Application (sNDA) dated July 12, 2013, received July 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doxil (doxorubicin HCl liposome injection), 20 mg/10 mL and 50 mg/25 mL.

We also refer to our November 12, 2013, Complete Response letter and to your September 22, 2014, proposed Complete Response, received September 22, 2014, to your supplemental new drug.

We refer to Comment #2 of our November 12, 2013, letter which states:

“In section ‘3.2.P.2.3 Manufacturing Process Development,’ the in vitro drug leakage and in vitro drug release assay under multiple pH conditions were assessed. However, the sample sizes, the variability in each test, the data for each individual unit and the similarity factor f_2 values were not provided. In your response, submit the following information:

- a. The sample sizes and individual data with the variability (standard deviation and/or CV) for each lot used in each of the drug leakage and the in vitro drug release tests.
- b. The similarity factor f_2 values for the profile comparisons using (b)
(4) units of each lot per test.

We have the following request for response regarding Comment 2(a) above:

- **Provide detailed information regarding the location of where the individual unit or replicate in-vitro release data can be found in the CTD files within the submission.**

Please provide a response via e-mail by 3:00 P.M., EST, Thursday, October 2, 2014, and follow with a formal submission to the NDA.

If you have any questions, please feel free to call me at 301-796-9022.

Sincerely,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

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/s/

ANUJA PATEL
09/30/2014

Patel, Anuja

From: Patel, Anuja
Sent: Friday, June 20, 2014 2:38 PM
To: 'Scurato, Matthew [JRDUS]'
Subject: FDA IR: Doxil Inquiry on Labeling Submission Prior to Response to CR NDA 50718_S 046 Resubmission

Importance: High

Dear Mr. Scurato,

We refer to our June 13, 2014 email communication requesting an update on the status of the BE Study DOXILNAP1002 and when you anticipate submitting a resubmission in response to our November 12, 2013 Complete Response letter.

We also refer to your June 17, 2014 email response in which you informed the FDA that you are currently targeting a submission in September 2014 for BE study DOXILNAP1002 and the complete response package.

We have the following request for you to send your proposed draft labeling and to provide your response via email only, no later than July 11, 2014:

- Please send via email tracked changes and clean WORD versions of your proposed labeling for your Package Insert in response to our November 12, 2013, Complete Response letter. We will conduct an **informal review** and provide **general clinical comments** to you via email. Please note however, a **formal review** of your package insert labeling will occur once we receive your proposed draft labeling with your resubmission.

Please acknowledge receipt and let me know if you have any additional questions.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Scurato, Matthew [JRDUS] [mailto:MSCURATO@ITS.JNJ.COM]
Sent: Tuesday, June 17, 2014 3:30 PM
To: Patel, Anuja
Subject: FW: Doxil Inquiry on Labeling Submission Prior to Response to CR NDA 50718?S 046)
Importance: High

Dear Anuja,

I am following up on this. We are currently targeting a submission in September for BE study DOXILNAP1002 and the complete response package.

We appreciate the Agency considering this and look forward to a response regarding submission and review of the label.

Regards
Matt Scurato



Janssen Research & Development, LLC
920 Route 202, P.O. Box 300
Raritan, NJ 08869
Phone: 908 704 5187

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From: Scurato, Matthew [JRDUS]
Sent: Friday, June 13, 2014 3:57 PM
To: 'Patel, Anuja'
Subject: RE: Doxil Inquiry on Labeling Submission Prior to Response to CR NDA 50718?S 046)

Hi Anuja
I am acknowledging receipt. I will get back to as soon as possible next week with a target submission date

Regards
Matt Scurato



Janssen Research & Development, LLC
920 Route 202, P.O. Box 300
Raritan, NJ 08869
Phone: 908 704 5187

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From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Friday, June 13, 2014 2:01 PM
To: Scurato, Matthew [JRDUS]
Subject: RE: Doxil Inquiry on Labeling Submission Prior to Response to CR NDA 50718?S 046)
Importance: High

Dear Mr. Scurato,

Thank you for your email sent May 30, 2014, regarding the possibility of our review of your label while you work on your response to the CR under Supplement 46. Please provide an update on the status of the BE Study DOXILNAP1002 and when you anticipate submitting a resubmission in response to our November 12, 2013 Complete Response letter. Once we receive your response we will be able to respond accordingly.

Please ack receipt.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
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/s/

ANUJA PATEL
06/20/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 21, 2013

From: Anuja Patel, M.P.H. Health Project Manager DOP2/OHOP

Subject: NDA 050718/S 046: Internal Labeling Meeting #2

Attendees:

Patricia Keegan, Marc Theoret, Meredith Chuk, Shawna Weis, Whitney Helms, Ann Marie Trentacosti (SEALD/PLR), Safaa Burns, Gene Williams, Otto Townshend (DMEPA), Anuja Patel, Robert Mellow, Christine Bina, Hasmukh Patel, Kavita Vyas, Mahesh Ramanadham, John Duan, Okpo Eridiri

Discussion During Meeting:

This meeting was previously scheduled as an internal labeling meeting to discuss CMC and carton container labeling. In addition to labeling, the team discussed and agreed to issue a Complete Response (CR) letter for this supplement and provide general labeling comments for the carton and container labeling and the package insert.

The following agreements were made:

- The team agreed to move up our planned action date to November 8 (PDUFA goal is November 12) due to the November 11 holiday.
- During the meeting, the team agreed to include comments for carton and container labeling in our CR letter. We also discussed the possibility of including labeling comments as an attachment rather than in-text proposed edits (which is currently under internal discussion with DOP 2 management).
- The team agreed that all pending reviews be uploaded in DARRTS by Friday, October 25, 2013.
- CMC Inspections Update on Form DIDQ will be provided by November 6 (or sooner).
- The team also discussed the proposed written responses to Janssen's meeting request submitted under NDA 50718 that are related to this supplement. The team agreed to issue our written responses after our action on supplement 46 and refer to our comments in the CR letter as a response to Question 5.

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ANUJA PATEL
11/08/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 17, 2013

From: Anuja Patel, M.P.H. Health Project Manager DOP2/OHOP

Subject: NDA 050718/S 046: Internal Labeling Meeting #1

FDA's proposed revisions as discussed during the October 17, 2013 labeling meeting.

Attendees:

Patricia Keegan, Marc Theoret, Meredith Chuk, Shawna Weis, Whitney Helms, Ann Marie Trentacosti (SEALD/PLR), Safaa Burns, Gene Williams, Otto Townshend (DMEPA), Anuja Patel

Discussion During Meeting:

Per the planning meeting that was held July 30, 2013, the review team agreed to review their relevant sections of the package insert and provide general comments that will be included as an attachment with the final action letter. A detailed review of the label was requested for specific disciplines only if there were specific changes proposed as part of this supplement.

The purpose of this first meeting was to review the clinical, pharm/tox, and clinical pharmacology sections of the label. In addition, we requested PLR review of the label with comments to be included (if any) in our action letter.

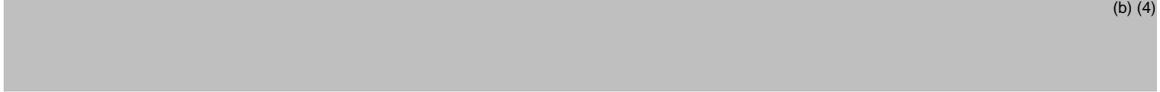
Sections covered included:

- Section 2.6: Patients With Hepatic Impairment
- Section 3: Dosage Forms and Strengths
- Section 5.6: Fetal Mortality changed to Embryofetal Toxicity
- Section 5.9: Secondary Oral Neoplasms
 - Clinical included recently approved text from the August 30, 2013 approval letter under supplement 045 as the Applicant did not amend labeling for supplement 046 as stated in the August 30, 2013 Approval letter.
- Section 6.3: Postmarketing Experience- deleted Secondary Neoplasms per the currently approved label version from Supplement 045
- Section 7: Drug Interactions
- Section 8: Use in Specific Populations
 - Added Sub-section for "Risk Summary" and "Animal Data"
- Section 8.3: Nursing Mothers
- Section 8.6: Females and Males Reproductive Potential
 - Proposed adding Sub-section "Contraception" for Females and Males to reflect and be consistent with the revised labeling for doxorubicin under NDA050629.
 - Proposed adding Sub-section "Infertility" for Females and Males to reflect the revised labeling for doxorubicin under Pfizer's NDA050629.

- Section 8.7: Hepatic Impairment

- Section 11: Description

-



(b) (4)

-

- Section 13.1: Carcinogenesis, Mutagenesis, and Impairment of Fertility

- Section 16: How Supplied/Storage and Handling

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/s/

ANUJA PATEL
11/08/2013

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 25, 2013
TIME: 2:00 PM to 3:00 PM
LOCATION: Teleconference, WO 22, Room 5313
APPLICATION: NDA 50718
DRUG NAME: Doxil
TYPE OF MEETING: Informal Teleconference (non-PDUFA meeting)

MEETING CHAIR: Patricia Keegan, M.D.

MEETING RECORDER: Anuja Patel, M.P.H

FDA ATTENDEES:

Patricia Keegan - DOP2 Director
Marc Theoret - DOP2 Clinical Team Leader
Meredith Chuk - DOP2 Clinical Team Leader
Monica Hughes - DOP2 CPMS
Anuja Patel - DOP2 RPM
Norma Griffin - DOP2 RPM
Kavita Vyas - ONDQA Product Quality Reviewer
John Duan - ONDQA Product Quality Reviewer
Robert Justice - DOP1 Director
Amna Ibrahim - DOP1 Deputy Director
Gwen Ison - DOP1 Clinical Reviewer
Mahesh Ramanadham - Office of Compliance
Christine Bina - Drug Shortage

JANSSEN ATTENDEES:

Craig L. Tendler, Vice President, Late Development and Global Medical Affairs
Roland Knoblauch, Senior Director, Clinical Oncology
Fitzroy Dawkins, Director, Clinical Oncology
Youn Choi Park, Director, Biostatistics
Trilok Parekh, Senior Director, Clinical Oncology
Naushad Islam, Director, Global Regulatory Affairs
Frank J. Deluccia, Vice President, Global CMC Regulatory Affairs
Barbara Kolb, North America Therapeutic Area Leader, Oncology
Hemal Morjaria, Senior Director, Global Regulatory Affairs
Kelly Johnson Reid, Director, Global Regulatory Affairs

MEETING PURPOSE: FDA requested this teleconference to clarify questions regarding Janssen's short term and long term plan to meet Doxil supply needs. In advance of this teleconference, FDA provided Janssen discussion points from Office of Drug Shortage, Office of Compliance, Office of Hematology and Oncology, and ONDQA on July 25, 2013. Our

discussion points, Janssen's responses, and the meeting summary are included in the Discussion section below.

BACKGROUND:

Doxil has been experiencing drug shortage issues to do issues with its contract manufacturer. Janssen submitted a Type A meeting request to the FDA on December 14, 2011, to seek the Agency's guidance on the path forward to expedite approval of replacement manufacturing facilities for Doxil. Janssen's meeting briefing package was received on December 15, 2011. In response to the FDA communications of January 11, 2012, for the short-term solution (part of the manufacturing process to occur at current contract manufacturer and finishing at a subsequent new manufacturer) and the FDA preliminary comments dated January 10, 2012, for the long term solution (entirely new manufacturing facility), Janssen provided slides for the face-to-face meeting on January 13, 2012, where both the long-term and short-term plans were discussed.

Janssen's February 10, 2012, submission contained a Protocol Element Document (PED) that outlined the design of a potential bioequivalence (BE) study intended to support the long-term plans for addressing Doxil shortages. On March 2, 2012, FDA provided an advice/information request letter with the following comments pertaining to the PED.

On March 20, 2013, Janssen submitted a Protocol Amendment (IND 036778 SD 623) for Protocol Number DOXILNAP1002, entitled "A Pivotal Bioequivalence Study of DOXIL/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies including Subjects with Ovarian Cancer, in support of a proposed new manufacturing facility for DOXIL." FDA issued an Information Request on April 25, 2013, in response to Janssen's March 20, 2013 submission requesting additional CMC information (i.e. type of equipment to be used to manufacture Doxil and clarification whether extended testing will be performed) on the proposed new manufacturing facility at the TTY Biopharm Co. Ltd facility in Chungli Taoyuan, Taiwan using the same process as BVL. Janssen submitted a response to our April 25, 2013 information request on April 30, 2013 (IND 036778 SD 629).

On May 24, 2013, FDA issued non hold CMC comments for Protocol DOXILNAP1002 which contained a request for data regarding the extended characterization studies performed on the batches made at proposed TTY facility and a request for data to support the suitability of the proposed stoppers for their intended use (for example, details of material of construction compared with approved stopper materials, and compatibility with Drug Product formulation including results of leachables and extractables study). Janssen submitted a response to the May 24, 2013 non hold comments on May 29, 2013 (SD 635).

On Janssen submitted

(b) (4)

(b) (4)

On July 12, 2013, Janssen submitted a supplemental new drug application (NDA 50718/046) that proposed a bioequivalence waiver for the addition of a new manufacturing site, TTY Biopharm Company Limited (TTY Biopharm) located in Chungli, Taoyuan, Taiwan, R.O.C. for the manufacturing process and (b) (4) operations of the drug product; change in batch size of the drug product –to (u) (4) for TTY; change in the specification for the containers and closures for the drug product to include (b) (4) stoppers; and addition of a secondary packaging site at (b) (4)

TELECONFERENCE DISCUSSION REGARDING FDA’S DISCUSSION POINTS:

Drug Shortage

1. What is Janssen’s current manufacturing status at BVL (b) (4)?

JANSSEN’S JULY 25, 2013 RESPONSE: Janssen discussed that they are considering in planning ahead to maintain DOXIL supply.

DISCUSSION DURING TELECONFERENCE: Janssen stated during the teleconference that Caelyx is as marketed in Europe; however, due to the stipulations in the BVL consent decree (effective January 31, 2013), Janssen can only release lots of Doxil through regulatory discretion from the FDA. At this time, Janssen was confident that BVL could continue to produce and supply Doxil.

Office of Compliance:

2. TTY Biopharm’s website states that the facility has been inspected by the United States, Office of Compliance requested additional information from TTY Biopharm to verify these statements; however, no response was received.

DISCUSSION DURING TELECONFERENCE: Janssen acknowledged FDA’s statement regarding TTY Biopharm’s website and stated that they will follow up with the TTY manufacturing facility. Janssen informed the FDA that Janssen had reached out to TTY facility and confirmed that it was inspected by German officials

but not the FDA. Janssen informed FDA that the TTY facility is ready for FDA inspection.

Office of Hematology and Oncology Products- Divisions of Oncology Products 1 and 2

3. Please clarify how Janssen will ensure continued Doxil drug supply for proposed

(b) (4)

(b) (4)

4. Please provide current status of the BE study DOXILNAP1002, entitled "A Pivotal Bioequivalence Study of DOXIL/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies Including Subjects with Ovarian Cancer, in support of a proposed new manufacturing facility for DOXIL" under IND 036778 for the Taiwan site (SDN 623 Protocol Received March 20, 2013).

a. Confirm that sufficient Doxil drug product (batch #5, Lot#1207529, be used as reference drug for the BE study, released under regulatory discretion as noted in our January 11, 2013, minutes) is available to complete the trial.

DISCUSSION DURING TELECONFERENCE: Janssen noted that the lot number referenced above was incorrect, it had been later updated via email communication on March 13, 2013, and that the correct lot number was Lot #1209506.

- b. When does Janssen plan on initiating enrollment for the BE study?

DISCUSSION DURING TELECONFERENCE: Janssen stated that the first patient was dosed in the ongoing BE study DOXILNAP1002, being conducted under IND 36778, on June 14, 2013. As of July 25, 2013, a total of 23 patients had been randomized of which 2 were non evaluable, 17 patients were no-ovarian cancer patients, and 7 patients had ovarian cancer. Per the protocol, 24 ovarian cancer patients need to be accrued in order to perform the initial analyses.

ONDQA

5. The July 12, 2013, a CMC PAS supplement (supplement 46) proposes minor labeling revisions, and contains data that Janssen proposes support a BE waiver for the proposed Taiwan manufacturing facility.
- a. Your request for a bioequivalence (BE) waiver is not acceptable. To qualify the new manufacturing site at TTY, Taiwan, a BE study is necessary. An animal study cannot substitute for a human BE study. You should conduct the BE study, as discussed under IND 36778, as planned in the previously provided study protocol (No. DOXILNAP1002).
- b. Please clarify when material from the Taiwan site will be ready for use in the BE study.

DISCUSSION DURING TELECONFERENCE: Janssen acknowledged FDA's comment 5 (a). Regarding 5(b), Janssen confirmed they had adequate lots of material from the TTY site to complete the BE study.

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/s/

ANUJA PATEL
11/08/2013

**Initial Planning Meeting Minutes
July 30, 2013**

Product: DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion
sNDA: 50718/S-046
(CMC Prior Approval Supplement with Manufacturing Changes)
eCTD submission: SDN 883

Submission Date: July 12, 2013
Received Date: July 12, 2013
Sponsor: Janssen Research & Development, LLC

Purpose: The purpose of this prior approval supplement is to request approval of the following changes:

- Addition of a manufacturing site (TTY BioPharm) for the manufacturing process of the drug product.
- Request for BE study waiver (Study DOXILNAP1002 initiated/ongoing)
- Change in batch size of the drug product - (b) (4) for TTY
- Change in the specification for the containers and closures for the drug product - (b) (4) Stoppers
- Addition of a secondary packaging site: (b) (4)
- Addition of nonclinical data in labeling

Currently Marketed Indications:

- **Ovarian cancer**
After failure of platinum-based chemotherapy.
- **AIDS-related Kaposi's**
After failure of prior systemic chemotherapy or intolerance to such therapy.
- **Multiple Myeloma**
In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

Current Review Team for sNDA 50718/S-045
(* denotes meeting attendees)

*Patricia Keegan, M.D., Director, DOP2
*Monica Hughes, M.S., CPMS, DOP2
*Anuja Patel, M.P.H., Regulatory Health Project Manager
*Marc Theoret, M.D., Clinical Team Leader (CDTL)
*Meredith Chuk, M.D., Medical Officer (DOP 2)
Whitney Helms, Ph.D., Non-Clinical (TL)
*Shawna Weis, Ph. D (Acting TL)
Alexander Putman, Non-Clinical
Angelica Durantes, Ph.D., Biopharmaceutics Team Leader, ONDQA
*John Duan, Ph. D., Biopharmaceutics Reviewer
*Hasmukh Patel, Ph.D., Acting Branch Chief
*Chidambaram Nallaperumalal, Ph.D.
*Kavita Vyas, CMC Reviewer
Jewell Martin, Product (ONDQA RPM)
Janice Pohlman, OSI TL

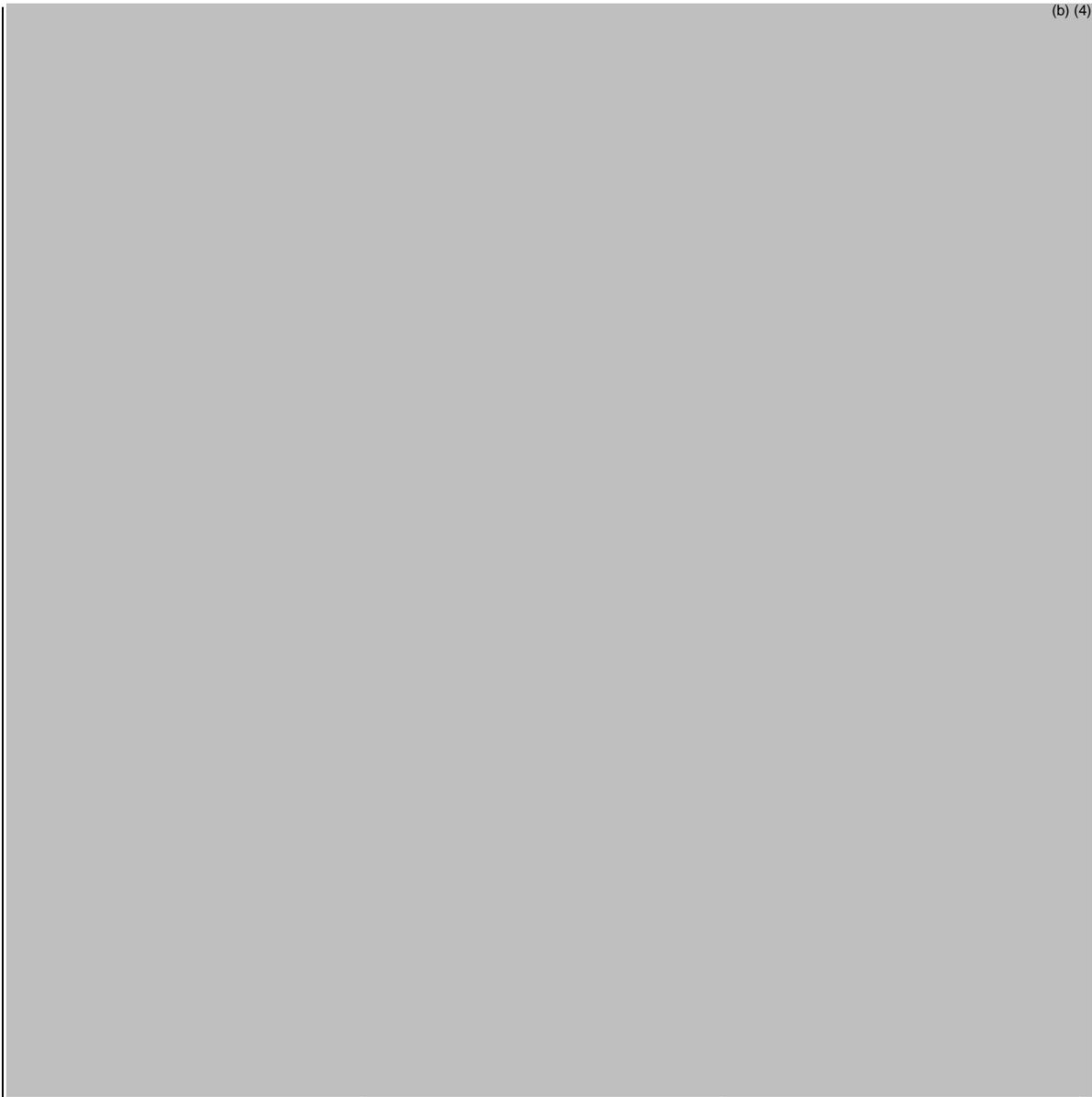
sNDA 50718/S-046 DOXIL (doxorubicin HCl liposome injection) for intravenous infusion
Initial Planning Meeting Minutes

Lauren Iacono-Connor, OSI Reviewer
Susan Thompson, OSI
*Mahesh Ramanadham, OC, OMPQ
*Sue Kang, OSE, Safety RPM
* Kevin Wright, DMEPA
Christine Bina, OC, Drug Shortage

Regulatory Background:

The tables below were provided to the review team as an overview.

Janssen's ^{(b) (4)} **Key FDA Regulatory Documents :**



IND 036778 Protocol Amendment (SDN 623)	Received March 20, 2013	Protocol Number DOXILNAP1002, entitled "A"
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sNDA 50718/S-046 DOXIL (doxorubicin HCl liposome injection) for intravenous infusion
Initial Planning Meeting Minutes

(BE Protocol)	FDA CMC Comments sent April 25, 2013 (Re: Request for clarification on manufacturing site TTY Biopharm Company Ltd (Taiwan site))	Pivotal Bioequivalence Study of DOXIL/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies including Subjects with Ovarian Cancer, in support of a proposed new manufacturing facility for DOXIL."
	FDA CMC Non-hold Comments sent May 24, 2013 (Re: Request for data on extended characterization studies performed on the batches made at proposed TTY facility; request for data to support suitability of proposed stoppers for their intended use)	
Citizen Petition- to adopt BE requirements for any ANDA or 505b(2) application for a liposomal doxorubicin product based on DOXIL	May 6, 2009	
Office of Generic Drugs- White Paper on development of liposomal doxorubicin	October 2009	
Office of Generic Drugs Issues Guidance on development of liposomal doxorubicin products	February 2010	
FDA Response to May 6, 2009 Citizen Petition	February 4, 2013	
DOP 1, DOP 2, ONDQA, OC Teleconference with Janssen to discuss Janssen's supply plans for the (b) (4) BE study under IND 036778	Informal Teleconference held July 25, 2013	Discussion regarding request for BE waiver, Status of Taiwan site regarding FDA inspections, enrollment update from Janssen re: BE study DOXILNAP1002

*A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Discussion Items:

1. **Review Status:** 4 Month Review Clock (Action Date: November 12, 2013)

Discussion During Meeting:

- Confirmed the signatory for this supplement: Dr. Keegan, DOP 2

- Noted that the clinical development of doxorubicin HCl liposome injection for intravenous infusion has been conducted under IND 036778
- Discussed the request for Waiver of BE study contained in this supplement
- Discussed the request for waiver of in vivo studies
- Discussed the non-clinical data that was submitted
- Minor proposed revisions in labeling submitted, copy of labeling was provided.
- Revised carton-container labeling was submitted for 20 mg and 50 mg, copy of carton—container was provided

The team discussed whether a BE waiver would be granted. The team agreed that a BE waiver will not be granted. Based on FDA Guidance, White Paper, and Citizen Petition, in order to establish bioequivalence a clinical BE study must be conducted and the clinical data must be submitted to support the proposed changes involving both manufacturing site and manufacturing process changes. The non-clinical toxicology data will be reviewed but are unlikely to be sufficient to serve in lieu of clinical data. .

2. Consults Submitted:

Discussion During Meeting: The review team discussed the following consults:

- OSE /DMEPA- Carton Container
- SEALD/PLR Review-if the team agrees to send general labeling comments regarding the current state of the PLR label, SEALD will be consulted.
- Clinical Pharmacology will be asked to perform a general review of Label
- CMC/Manufacturing site Inspections (EES)
- Microbiology Consult
- OPDP
- CMC/Jewell Martin will assist with the following consults:
 - Establishment (EES)/Coordinate Inspections
 - Environmental Analysis: Request for Categorical Exclusion
 - Labeling

DISCUSSION DURING MEETING: On July 25, 2013, DOP 2, DOP 1, ONDQA, ODS, and OC held an informal (non-PDUFA) teleconference. Janssen informed the FDA that the TTY Biopharm manufacturing facility in Taiwan has not been inspected by the U.S., as previously reported on their website; however, the site was ready for inspections. Janssen further clarified that the ongoing BE study Protocol DOXILNAP1002, entitled, "A Pivotal Bioequivalence Study of DOXIL/CAELYX® Manufactured at a New Site in Subjects with Advanced or Refractory Solid Malignancies including Subjects with Ovarian Cancer, in support of a proposed new manufacturing facility for DOXIL" had its first patient dosed on June 14, 2013.

3. Upcoming/TBD Internal Team Meetings:

- a. **Filing Meeting:** None
- b. **Labeling Meetings : 2 scheduled**

Discussion During Meeting: After reviewing the labeling in its current PLR state, the team proposed to use 4 month review period to review and make high level general comments to the package insert and carton and container labeling and

sNDA 50718/S-046 DOXIL (doxorubicin HCl liposome injection) for intravenous infusion
Initial Planning Meeting Minutes

agreed to hold two labeling meetings. The first meeting will include Clinical, Pharm/Tox, and Clinical Pharmacology. The second labeling meeting will include CMC and Carton Container labeling. In addition, the team agreed that since Doxil is not formatted properly in PLR format that a PLR review will be needed. While the team plans to issue a Complete Response (CR) letter, FDA will be sending general labeling comments for the package insert and carton and container.

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ANUJA PATEL
11/02/2013

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Anuja Patel/RPM, OHOP/DOP 2/301-796-9022
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REQUEST DATE 10.29.2013	IND NO.	NDA/BLA NO. NDA 50718/S-046	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Doxil (doxorubicin HCl liposome injection)	PRIORITY CONSIDERATION PAS with Manufacturing (4 months)	CLASSIFICATION OF DRUG Anthracycline antibiotic	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) October 25, 2013
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NAME OF FIRM: Janssen	PDUFA Date: November 12, 2013 (Planned Action: November 8, 2013)
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TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
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EDR link to submission:
EDR Location: <\\CDSESUB1\evsprod\NDA050718\050718.enx> (SDN 883)

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

DOP 2 requests OPDP review of the carton container label. Planned action is November 8, 2013 therefore a review is requested by November 5, or sooner.

SIGNATURE OF REQUESTER Anuja Patel	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> eMAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	

06/18/2013

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ANUJA PATEL
10/29/2013

INSPECTIONAL ASSIGNMENT (EMAIL TRANSMITTAL)

Date: September 19, 2013

To: Division of Medical Products and Tobacco Inspections
Office of Regulatory Affairs

Facility: TTY Biopharm Co. Ltd.
838, Sec. 1 Chung-HWA Road
Chung-Li, Taoyuan, Taiwan
FEI No.: 3005054986

**Drug Name
(dosage form,
strength/concentration):** Doxorubicin Hydrochloride Liposome Injection, 2mg/mL,
10 mL and 25 mL

Profile Class: SVS

A/NDA No.: NDA 50-718, Supplement 046

Chemistry Reviewer Kavita Vyas, Ph.D.
CDER/OPS/ONDQA/DNDQAI/BRIII
kavita.vyas@fda.hhs.gov Tel: 301-796-4787

**Microbiology Reviewer (if
applicable)** Robert J. Mello, Ph.D.
OMPT/CDER/OPS/NDMS
Robert.Mello@fda.hhs.gov Tel: 301-796-1574

OC Compliance Officer Vipul Dholakia, Ph.D.
CDER/OC/OMPQ HFD-320
vipul.dholakia@fda.hhs.gov Tel. 301-796-5065

CDER has identified specific area(s) for inspectional focus for drug product manufacturing in connection with the NDA 50-718, Supplement 046. In accordance with the Pre-Approval Inspection Program Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of drug product by focusing on areas in which data is questionable; drug characteristics or sensitivities¹ indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

¹ Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size, or other physical characteristics

Summary of Product and Manufacturing Process:

Background:

Janssen Research & Development, LLC (Janssen) is the sponsor for NDA 50-718. The manufacturing process for DOXIL was originally developed by ALZA Corporation (ALZA). Janssen and ALZA are both wholly owned subsidiaries of Johnson & Johnson. DOXIL has been contract manufactured at Ben Venue Laboratories (BVL), Bedford, Ohio for Janssen since 1995. As a result of entering into a consent decree with the FDA, Ben Venue Laboratories' (BVL) has ceased manufacturing all sterile products including Doxil®. In order to restore Doxil supplies, Janssen has filed NDA 50-718, Supplement 046 that provides for an alternate manufacturing site for Doxil, TTY Biopharm Co. Ltd. (TTY), in Taiwan (the site that is relevant to this inspection). Janssen intends to manufacture Doxil (batch size (b) (4)) at this site using the same manufacturing process as BVL (batch size (b) (4)) with equivalent equipment and the same quality of drug substance and excipients.

Product Description and Dosage Form:

Doxorubicin hydrochloride liposome injection is indicated for the treatment of patients with AIDS-related Kaposi's sarcoma, for treatment of patients with ovarian cancer, and for the treatment of patients with multiple myeloma (in combination with bortezomib).

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, is a sterile, red, translucent aqueous suspension of liposomes containing doxorubicin hydrochloride, 2mg/mL, in single (b) (4) vials (20mg/10 mL in a 10mL vial and 50mg/25 mL in a 30mL vial) for intravenous administration. The drug product is packaged in (b) (4) stopper and an (b) (4).

The quantitative and qualitative composition of the drug product is given in the following Table:

Component	Quality Reference	Function	Quantity (mg/mL) ^a
Doxorubicin Hydrochloride ^b	(b) (4)	Active	2.00
N-(Carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)	(b) (4)	(b) (4)	3.19
Fully hydrogenated soy phosphatidylcholine (HSPC)	(b) (4)	(b) (4)	9.58
Cholesterol	(b) (4)	(b) (4)	3.19
Ammonium Sulfate ^c	(b) (4)	(b) (4)	(b) (4)
Sucrose	(b) (4)	(b) (4)	(b) (4)
Histidine	(b) (4)	Buffer	(b) (4)
Hydrochloric Acid ^d	(b) (4)	(b) (4)	(b) (4)
Sodium Hydroxide ^d	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
(b) (4)			

Manufacturing Process:

(b) (4)

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/s/

VIPULCHANDRA N DHOLAKIA
09/23/2013

MAHESH R RAMANADHAM
09/23/2013



NDA 50718/S-046

INFORMATION REQUEST

Janssen Research & Development, LLC
on behalf of Janssen Products, L.P.
Attention: Naushad Islam, M.S., R.Ph.
Director, Global Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Dear Mr. Islam:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxil (doxorubicin HCl liposome Injection).

We also refer to your submission dated July 12, 2013.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 30, 2013, in order to continue our evaluation of your supplemental application.

1. Concerning the (b) (4) validation, provide the following additional information:

(b) (4)

If you have questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Branch Chief, Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HASMUKH B PATEL
08/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Anuja Patel, RPM/ OHOP/DOP2 301-796-9022		
DATE 8.12.2013	IND NO.	NDA NO. 50718/S-046	TYPE OF DOCUMENT sNDA	DATE OF DOCUMENT 7.12.2013
NAME OF DRUG Doxil (doxorubicin HCl liposome injection) intravenous infusion		PRIORITY CONSIDERATION PAS with Manufacturing Changes (4 months)	CLASSIFICATION OF DRUG anthracycline antibiotic	DESIRED COMPLETION DATE 10.11.2013
NAME OF FIRM: Janssen				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input checked="" type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton Container Labeling				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
EDR Location (SDN 883): \\CDSESUB1\evsprod\NDA050718\050718.enx				
REASON(S) FOR CONSULT / COLLABORATIVE REVIEW REQUEST:				
<ul style="list-style-type: none"> Assign reviewers to attend milestone and team meetings. Reviewers Assigned on 7.25.13: Yelena Maslov (TL) and Kevin Wright (Safety Evaluator) We are requesting review of carton and container labeling for supplement 46, which provides for a new manufacturing facility in Taiwan. Attend a separate labeling meeting with ONDQA and Biopharmaceutics to review CMC sections of label – Labeling Meeting to be scheduled 				

SIGNATURE OF REQUESTER Anuja Patel	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ANUJA PATEL
08/12/2013



NDA 50718/S-046

INFORMATION REQUEST

Janssen Research & Development, LLC
on behalf of Janssen Products, L.P.
Attention: Naushad Islam, M.S., R.Ph.
Director, Global Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Dear Mr. Islam:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxil (doxorubicin HCl liposome Injection).

We also refer to your submission dated July 12, 2013.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by August 16, 2013, in order to continue our evaluation of your supplemental application.

(b) (4)

If you have questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Branch Chief, Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HASMUKH B PATEL
08/07/2013



NDA 50718/S046

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Janssen Products, L.P.
Attention: Naushad Islam, M.S., R.Ph.
Director, Global Regulatory Affairs
Janssen Research & Development LLC
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

Dear Mr. Islam:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 050718

SUPPLEMENT NUMBER: 046

PRODUCT NAME: DOXIL® (Doxorubicin HCl liposome injection), for intravenous infusion, single (b) (4) vial: 20 mg/10 mL and 50 mg/25 mL

DATE OF SUBMISSION: July 12, 2013

DATE OF RECEIPT: July 12, 2013

This supplemental application proposes the addition of a new manufacturing facility, TTY Biopharm Company Limited in Chungli, Taoyuan, Taiwan and revisions to the carton and container labels to include the new manufacturer information.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 10, 2013, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be November 12, 2013.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call Anuja Patel, Regulatory Health Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Monica Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
08/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO (Division/Office): **New Drug Microbiology Staff**

E-mail to: CDER OPS IO MICRO
Paper mail to: WO Bldg 51, Room 4193

FROM: **Jewell Martin**

PROJECT MANAGER (if other than sender):

REQUEST DATE
7/29/2013

IND NO.

NDA NO.
NDA
50718/S046

TYPE OF DOCUMENT
sNDA

DATE OF DOCUMENT
7/12/2013

NAMES OF DRUG

Doxil

PRIORITY CONSIDERATION

PAS

PDUFA DATE

11/12/2013

DESIRED COMPLETION DATE

9/12/2013

NAME OF APPLICANT OR SPONSOR: **Janssen**

GENERAL PROVISIONS IN APPLICATION

- | | |
|---|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED | <input type="checkbox"/> CBE-0 SUPPLEMENT |
| <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____ | <input type="checkbox"/> CBE-30 SUPPLEMENT |
| <input type="checkbox"/> BUNDLED | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input type="checkbox"/> DOCUMENT IN EDR | |

COMMENTS / SPECIAL INSTRUCTIONS:

Requesting microbiology review for 50718/S-046 – Provides for an additional facility, TTY Biopharm located in Taiwan for the manufacture of DOXIL

Bob Mello has been working on this application/shortage.

Indication: oncology

Chemistry reviewer: Kavita Vyas

Please send the name of assigned reviewer to ONDQA PM – Jewell Martin

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS EDR E-MAIL MAIL HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

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/s/

JEWELL D MARTIN
07/29/2013