

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-763

Chemistry Review(s)

NDA 50-763

Mitozytrex (Mitomycin for Injection)

SuperGen, Inc.

Yung-Ao Hsieh, Ph.D.

Division of Oncology Drug Products

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Chemistry Review Data Sheet

1. NDA 50-763 Resubmission
2. REVIEW No.: 2
3. REVIEW DATE: 12-Nov-02
4. REVIEWER: Yung-Ao Hsieh, Ph.D.

5. PREVIOUS DOCUMENTS:

| <u>Submissions</u> | <u>Document date</u> |
|--------------------|----------------------|
| Original | 12-Dec-97 |
| Amendment BC | 13-Mar-98 |
| Amendment AZ | 20-Mar-02 |
| Amendment AZ | 13-May-02 |
| Amendment BL | 21-May-02 |
| Amendment BC | 12-Jun-02 |
| Amendment BC | 13-Jun-02 |

6. SUBMISSIONS BEING REVIEWED:

| <u>Submission</u> | <u>Document date</u> |
|-------------------|----------------------|
| Amendment BC | 4-Oct-02 |
| Amendment BC | 21-Oct-02 |
| Amendment BC | 4-Nov-02 |

7. NAME & ADDRESS OF APPLICANT:

Name: SuperGen Inc.

Address: 4140 Dublin Boulevard, Dublin, CA 94568

Representative: Sam Boddapati, Senior Director, Regulatory Affairs

Telephone: 925-560-0100

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mitozytrex™
Established Name: Mitomycin, USP for Injection
Chem. Type/Submission Priority:
 - Chem. Type: antitumor antibiotics
 - Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a DNA alkylating agent

11. DOSAGE FORM: sterile, — powder

12. STRENGTH/POTENCY: 5 mg

13. ROUTE OF ADMINISTRATION: intravenous infusion

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS products – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

Chemical Name: [1aR-(1 α , 8 β , 8 α , 8 β)]-6-amino-8-[[aminocarbonyl]oxy]methyl]-1, 1a, 2,

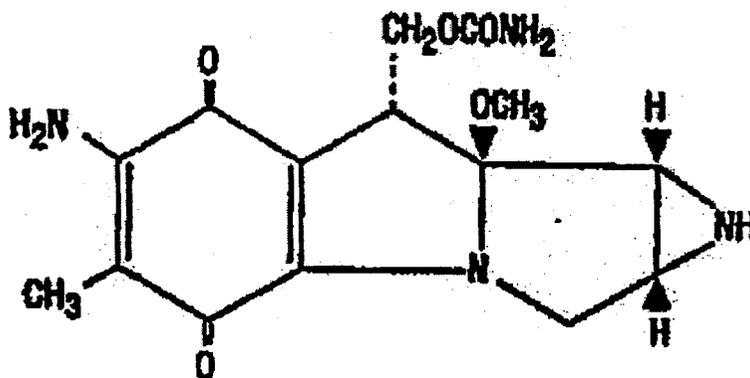
8, 8a, 8b-hexahydro-8a-methoxy-5-methyl azirino[2', 3':3, 4]pyrrolo [1, 2-a] indole-4,7-dione

Alternate Name: Mitomycin [50-07-7]

Molecular Formula: C₁₅H₁₈N₃O₅

Molecular Weight: 334.33

Structural Formula:



17. RELATED SUPPORTING DOCUMENTS: N/A

18. CONSULT STATUS:

| Consults/CMC Related reviews | Recommendation | Date | Reviewer |
|------------------------------|----------------|-----------|----------------|
| EES | Acceptable | 20-Sep-02 | |
| Microbiology | Approval | 02-Jul-02 | James L. Mcvey |

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 50-763

The Executive Summary

I. Recommendations:

The application is recommended for approval from a chemistry point of view.

II. Summary of Chemistry Assessments:

A. Description of the Drug Product and Drug Substance:

The active ingredient is mitomycin of USP compendial grade. Mitozytrex is a sterile, — powder containing mitomycin C (5 mg) formulated with 2-hydroxypropyl- β -cyclodextrin (2 g). It should be reconstituted with Water for Injection prior to intravenous administration. The drug product can be stored at 25°C/60% RH. Adequate stability data have been provided to support the requested expiration dating of two years.

B. Description of How the Drug Product is Intended to be Used

Mitozytrex is not recommended as single-agent, primary therapy. Mitomycin has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.

C. Basis for Approvability Recommendation

Responses provided in amendments BC dated 21-Oct-02 and 4-Nov-02 have satisfactorily resolved all of the CMC deficiencies identified in Review No. 1. From a chemistry viewpoint approval is recommended.

APPEARS THIS WAY
ON ORIGINAL

Administrative
A. Reviewer's Signature

YAH

Review Chemist, HFD-150
Yung-Ao Hsieh, Ph.D.

B. Endorsement Block

Y. A. Hsieh, Review Chemist:
R. H. Wood, Chemistry Team Leader:
B. Atkins, Project Manager:

C. CC Block

Original NDA 50-763
HFD-150 Div. File
HFD-150/YAHsieh
HFD-150/RHWood
HFD-150/ BAtkins

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/s/

Yung-Ao Hsieh
11/12/02 10:50:41 AM
CHEMIST

Rebecca Wood
11/12/02 10:56:47 AM
CHEMIST



NDA 50-763

MITOExtra (Mitomycin for Injection)

SuperGen, Inc.

Yung-Ao Hsieh, Ph.D.

Division of Oncology Drug Products

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| C. Basis for Approvability | 6 |
| III. Administrative | 7 |
| A. Reviewer's Signature | 7 |
| B. Endorsement Block | 7 |
| C. CC Block | 7 |
| Chemistry Assessment | 8 |
| I. Review of Common Technical Document-Quality Module 3.2 | 8 |
| Amendment AZ (13-May-02, Applicant's Responses to CMC | 8 |
| Deficiencies Listed in the NA Letter Dated 11-Dec-98) | |
| II. Review of Common Technical Document-Quality Module 1 | 24 |
| A. Amendment BL (21-May-02, Labeling and Package Insert) | 24 |
| B. Amendment BC (13-Jun-02 (Claim of Categorical Exclusion) | 25 |
| III. List of deficiencies to be Communicated | 25 |

Chemistry Review Data Sheet

1. NDA 50-763 Resubmission
2. REVIEW No.: 1
3. REVIEW DATE: 21-Aug-02
4. REVIEWER: Yung-Ao Hsieh, Ph.D.

5. PREVIOUS DOCUMENTS:

| <u>Submissions</u> | <u>Document date</u> |
|--------------------|----------------------|
| Original | 12-Dec-97 |
| Amendment BC | 13-Mar-98 |

6. SUBMISSIONS BEING REVIEWED:

| <u>Submissions Reviewed</u> | <u>Document date</u> |
|-----------------------------|----------------------|
| Amendment AZ | 20-Mar-02 |
| Amendment AZ | 13-May-02 |
| Amendment BL | 21-May-02 |
| Amendment BC | 12-Jun-02 |
| Amendment BC | 13-Jun-02 |

7. NAME & ADDRESS OF APPLICANT:

Name: SuperGen Inc.

Address: 4140 Dublin Boulevard, Dublin, CA 94568

Representative: Sam Boddapati, Senior Director, Regulatory Affairs

Telephone: 925-560-0100

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) **Proprietary Name:** MITOExtra™
Established Name: Mitomycin, USP for Injection
Chem. Type/Submission Priority:
 - Chem. Type: antitumor antibiotics
 - Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a DNA alkylating agent

11.DOSAGE FORM: sterile, — powder

12.STRENGTH/POTENCT: 5 mg

13.ROUTE OF ADMINISTRATION: intravenous infusion

14.Rx/OTC DISPENSED: x Rx OTC

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

SPOTS products – Form Completed

x Not a SPOTS product

16.CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

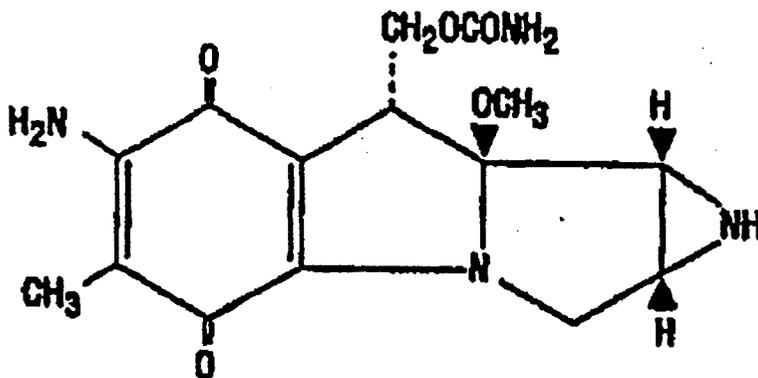
Chemical Name: [1aR-(1a α , 8 β , 8a α , 8b β)]-6-amino-8-[[[(aminocarbonyl)oxy]methyl]-1, 1a, 2, 8, 8a, 8b-hexahydro-8a-methoxy-5-methyl azirino[2', 3':3, 4]pyrrolo [1, 2-a] indole-4,7-dione

Alternate Name: Mitomycin C [50-07-7]

Molecular Formula: C₁₅H₁₈N₃O₅

Molecular Weight: 334.33

Structural Formula:



17.RELATED SUPPORTING DOCUMENTS: N/A

18. CONSULT STATUS:

| Consults/CMC Related reviews | Recommendation | Date | Reviewer |
|------------------------------|----------------|-----------|----------------|
| EES | Pending | | |
| OPDRA | Pending | | |
| Microbiology | Approval | 02-Jul-02 | James L. Mcvey |

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for NDA 50-763

The Executive Summary

I. Recommendations:

The application is approvable from a chemistry point of view.

II. Summary of Chemistry Assessments:

A. Description of the Drug Product and Drug Substance:

The active ingredient is mitomycin C of USP compendial grade. MITOExtra is a sterile, — powder containing mitomycin C (5 mg) formulated with 2-hydroxypropyl- β -cyclodextrin (2 g). It should be reconstituted with Water for Injection prior to intravenous administration. The drug product can be stored at 25°C/60% RH. The requested expiration dating of two years is supported by insufficient data.

B. Description of How the Drug Product is Intended to be Used

MITOExtra is not recommended as single-agent, primary therapy. Mitomycin has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.

C. Basis for Approvability Recommendation

NDA 50-763, was submitted 12-Dec-97 as a Type 3S NDA. An NA Letter, citing 43 deficiencies, was issued on 11-Dec-98. Amendment AZ (dated 20-Mar-02) addresses the deficiencies listed in the NA letter (CMC deficiencies: Items 9 through 32). Additional information and data were provided in the following amendments:

Amendment AZ (dated 13-May-02):

more clinical data and a revised package insert

Amendment BL, dated 21-May-02:

markups of vial carton and label

Amendment BC of 12-Jun-02:

updated list of manufacturing sites and analytical laboratories

Amendment BC dated 13-Jun-02:

a Claim for Categorical Exclusion from the Environmental Assessment

From a chemistry view point, this application is approvable. The CMC deficiencies listed in pages 25 and 26 of this review should be satisfactorily resolved before the application can be approved.

Administrative

A. Reviewer's Signature



Review Chemist, HFD-150
Yung-Ao Hsieh, Ph.D.

B. Endorsement Block

Y. A. Hsieh, Review Chemist:
R. H. Wood, Chemistry Team Leader:
B. Atkins, Project Manager:

C. CC Block

Original NDA/50-763
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/s/

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Rebecca Wood
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CHEMIST