Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 21,248

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<th>DOCUMENT DATE</th>
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NAME & ADDRESS OF APPLICANT: Cell Therapeutics, Inc.
201 Elliott Ave. W. 400
Seattle, WA 98119

DRUG PRODUCT NAME:
Proprietary: TRISENOX
Nonproprietary/USAN: Arsenic trioxide
Code Name/#: 1-P
Chem. Type/Ther. Class: 1-P

PHARMACOL. CATEGORY/INDICATION:
Treatment of acute promyelocytic leukemia (APL)

DOSAGE FORM/STRENGTHS:
1 mg/mL

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

As₂O₃, MW = 197.8, Arsenic trioxide
CAS 1327-53-3

SUPPORTING DOCUMENTS:

CONSULTS:

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<td>EES</td>
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<td>All sites for manufacture as well as testing are found to be acceptable.</td>
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<td>Microbiology</td>
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<td>Trademark</td>
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<tr>
<td>Environment Assessment</td>
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<td>USAN</td>
<td>arsenic trioxide</td>
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REMARK/COMMENTS:
The applicant has provided the updated information regarding the minor deficiencies and comments for the drug substance and drug product. The information is found to be adequate.

CONCLUSIONS AND RECOMMENDATIONS:
The NDA is recommended for approval from a chemistry manufacturing and control perspective.

See attached review notes.

/S/ 8/14/00
Xiaohong Chen, Ph.D., Review Chemist

/S/ 8/14/00
Chengyi Liang, Ph.D., Review Chemist

/S/ 8/14/00
Eric Duffy, Ph.D.
Chemistry Team Leader
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 21,248
SUBMISSION TYPE: Original

CHEM. REVIEW #: 1
DOCUMENT DATE: 3-27-2000

REVIEW DATE: 6-20-2000
CDER DATE: 3-28-2000
ASSIGN DATE: 4-3-2000

NAME & ADDRESS OF APPLICANT:
Cell Therapeutics, Inc.
201 Elliott Ave. W. 400
Seattle, WA 98119

DRUG PRODUCT NAME:
Proprietary: [Provisional]
Nonproprietary/USAN: proposed
Code Name/#: TBU
Chem. Type/Ther. Class: 1-P

PHARMACOL. CATEGORY/INDICATION:
Treatment of acute promyelocytic leukemia (APL)

DOSAGE FORM/STRENGTHS:
1 mg/mL

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
As₂O₃, MW = 197.8, Arsenic trioxide
CAS 1327-53-3
SUPPORTING DOCUMENTS:

CONSULTS:

Consult  Status  Comments
EES      Acceptable  Only manufacturer in  is pending for inspection. Other sites for manufacture and testing are found to be acceptable.

Microbiology  Acceptable  Submitted on 3/29/00
Trademark  Pending
Environment Assessment  Categorical exclusion  Acceptable
USAN  Pending

REMARK/COMMENTS:
Adequate CMC information has been submitted for this orphan drug which is used to treat acute promyelocytic leukemia (APL). Several minor deficiencies which are related to  and  studies need be resolved by the applicant.

CONCLUSIONS AND RECOMMENDATIONS:
The NDA is recommended for approval from a chemistry manufacturing and control perspective. The CMC deficiencies listed in the Draft Letter to the applicant will be sent as an information request. Response to the questions should be provided as soon as possible.

See attached review notes and draft deficiency letter.

Xiaohong Chen, Ph.D., Review Chemist

Chengyi Liang, Ph.D., Review Chemist
CC:
Orig. NDA 21-248
HFD-150 Division File
HFD-150/XChen
HFD-150/CLiang
HFD-150/EDuffy
HFD-150/DSpillman
HFD-810/Directors
REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 21-248
24 April 2000

A. 1. NDA 21-248
   APPLICANT:  Cell Therapeutics, Inc.
               201 Elliott Avenue, West
               Suite #400
               Seattle, WA  98119

   2. PRODUCT NAMES:  (arsenic trioxide injection)

   3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
      The product is intended for intravenous infusion.

   4. METHODS OF STERILIZATION:

   5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
      INDICATION:
      The drug product is indicated for the treatment of acute promyelocytic
      leukemia (APL).

B. 1. DATE OF INITIAL SUBMISSION:  27 March 2000

   2. DATE OF AMENDMENT:  (none)

   3. RELATED DOCUMENTS:

   4. ASSIGNED FOR REVIEW:  19 April 2000

C. REMARKS:
D. CONCLUSIONS: The application is recommended for approval, pending the applicant's commitment to provide the data indicated in "List of Microbiology Comments" post-approval.

/S/

24 Apr 2000

Paul Stinavage, Ph.D.

5/2/00

cc: Original NDA 21-248
    HFD-805/Stinavage/Consult File
    HFD-150/Div File/E. Duffy/C. Liang/D. Spillman

Drafted by: P. Stinavage, 24 April 2000
R/D initialed by P. Cooney
REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW #2 OF NDA 21-248
14 August 2000

A. 1. NDA 21-248 BZ
   APPLICANT: Cell Therapeutics, Inc.
   201 Elliott Avenue, West
   Suite #400
   Seattle, WA 98119

2. PRODUCT NAMES: (arsenic trioxide injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is intended for intravenous infusion.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is indicated for the treatment of acute promyelocytic leukemia (APL).

B. 1. DATE OF INITIAL SUBMISSION: 27 March 2000

2. DATE OF AMENDMENT: 11 July 2000 (Subject of this Review.)

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 14 August 2000

C. REMARKS:
D. CONCLUSIONS: This submission provides the data requested in Microbiologist's Review #1 dated 24 April 2000. The application is recommended for approval on the basis of sterility assurance.

cc: Original NDA 21-248  
    HFD-805/Stinavage/Consult File  
    HFD-150/Div File/E. Duffy/C. Liang/D. Spillman/X. Hong

Drafted by: P. Stinavage, 24 April 2000  
R/D initialed by P. Cooney
REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW #1 OF NDA 21-248
24 April 2000

A. 1. NDA 21-248
   APPLICANT:  Cell Therapeutics, Inc.
               201 Elliott Avenue, West
               Suite #400
               Seattle, WA  98119

2. PRODUCT NAMES:  (arsenic trioxide injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
   The product is intended for intravenous infusion.

4. METHODS OF STERILIZATION:  

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
   INDICATION:
   The drug product is indicated for the treatment of acute promyelocytic
   leukemia (APL).

B. 1. DATE OF INITIAL SUBMISSION:  27 March 2000

2. DATE OF AMENDMENT:  (none)

3. RELATED DOCUMENTS:  

4. ASSIGNED FOR REVIEW:  19 April 2000

C. REMARKS:  


D. CONCLUSIONS: The application is recommended for approval, pending the applicant's commitment to provide the data indicated in "List of Microbiology Comments" post-approval.

/S/
Paul Stinavage, Ph.D.
24 Apr 2000

cc: Original NDA 21-248
HFD-805/Stinavage/Consult File
HFD-150/Div File/E. Duffy/C. Liang/D. Spillman

Drafted by: P. Stinavage, 24 April 2000
R/D initialed by P. Cooney