CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-794

Chemistry Review(s)
NDA 50-794

Vidaza™
(Azacitidine for Injectable Suspension)

Planar Representation

Pharmion Corporation

Dr. Shan Hsieh, Ph.D.
Division of Oncology Drug Products,
HFD-150
# Table of Contents

Chemistry Review Data Sheet ................................................................. 3

Executive Summary .............................................................................. 7

Chemistry Assessment .......................................................................... 10

   S  DRUG SUBSTANCE [Name, Manufacturer] ........................................... 10
   P  DRUG PRODUCT [name, dosage form] ............................................... 58
   A  APPENDICES .................................................................................. 105
   R  REGIONAL INFORMATION .............................................................. 106

II. Review Of Common Technical Document-Quality (CTD–Q) Module 1 .......... 106
   A. Labeling & Package Insert ............................................................ 106
   B. Environmental Assessment Or Claim Of Categorical Exclusion .......... 107

III. List Of Deficiencies To Be Communicated ........................................ 108

Appears this way on original
Chemistry Review Data Sheet

1. NDA:  

2. REVIEW:  1

3. REVIEW DATE:  29-Apr-2004

4. REVIEWER:  Li-Shan Hsieh, Ph. D.

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND 64,251 N-015, (IC)</td>
<td>06-Jan-2003</td>
</tr>
<tr>
<td>IND 64,251 N-025 (IC)</td>
<td>23-Apr-2003</td>
</tr>
</tbody>
</table>

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>23-Mar-2003</td>
</tr>
<tr>
<td>Amendment 002, BC</td>
<td>12-Mar-2004</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

Name: Pharmion Corporation
Address: 2525 25th Street, Boulder, CO 80301
Representative: Gillian Iver-Read, Vice President, Clinical Development and Regulatory
Telephone: 720-564-9100, Fax: 720-564-9191

8. DRUG PRODUCT NAME/CODE/TYP:

a) Proprietary Name: Vidaza™
b) Non-Proprietary Name (USAN): Azacitidine
c) Code Name/# (ONDC only): CAS# 320-67-2
d) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type: 1
   • Submission Priority: P
9. LEGAL BASIS FOR SUBMISSION:
Paragraph 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act 21 CFR 314.50 and 21 CFR 314 Subpart H Orphan drug designation (Designation Request #01-1501)
Exclusive marketing rights: Section 527 of the FFDCA (21 U.S.C. 360 cc)

10. PHARMACOL. CATEGORY:
Antimetabolite, inhibitor of DNA methyltransferase and of uridine kinase for the Treatment of All Subtypes of Myelodysplastic Syndromes

11. DOSAGE FORM: Injectable suspension

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _xx_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
____SPOTS product – Form Completed
__xx_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical name: 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one
4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one
IUPAC Name: (2R,3R,4S,5R)-4-amino-1-(3,4-dihydroxy-5-hydroxymethyl-tetrahydrofuran-yl)-1H-[1,3,5]triazin-2-one
Molecular Formula: C$_8$H$_{12}$N$_4$O$_5$, Relative Molecular Mass: 244.20

17. RELATED/SUPPORTING DOCUMENTS:
IND 64,251 and IND 7574
A. DMFs:
<table>
<thead>
<tr>
<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>NCI</td>
<td>Clinical Information</td>
<td>7</td>
<td>N/A</td>
<td>N/A</td>
<td>No CMC information</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>Ben Venue Laboratories</td>
<td></td>
<td>1</td>
<td>Adequate</td>
<td>12-Mar-2004</td>
<td>Review by Dr. Marla Stevens-Riley</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
<td></td>
<td>1</td>
<td>Adequate</td>
<td>02-Apr-2004</td>
<td>Reviewed by Dr. Hossein Khorshide</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
<td></td>
<td>3</td>
<td>Adequate</td>
<td>05-Jul-2000</td>
<td>Reviewed by Dr. Chong-Ho Kim</td>
</tr>
</tbody>
</table>

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents: N/A

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>

18. STATUS:

ONDC:

<table>
<thead>
<tr>
<th>CONSULTS/ CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiology (sterility assurance)</td>
<td>Approval</td>
<td>23-Apr-2004</td>
<td>Paul Stinavage, HFD-805</td>
</tr>
<tr>
<td>EES</td>
<td>Acceptable</td>
<td>13-Feb-2004</td>
<td>S. Adams, HFD-122</td>
</tr>
<tr>
<td>ODS</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>Adequate</td>
<td>28-Apr-2004</td>
<td>Shwu-Luan Lee, HFD-150</td>
</tr>
<tr>
<td>Biopharm</td>
<td></td>
<td></td>
<td>Sophia Abraham, HFD-150</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>Adequate</td>
<td>29-Apr-2004</td>
<td>Li-Shan Hsieh, HFD-150</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CMC statistics)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 50-794

Executive Summary

I. Recommendations

A. Conclusion and recommended action
CMC information provided has been reviewed and found adequate. The Office of Compliance provided an overall acceptable recommendation on 13-Feb-2004 for all submitted sites. Therefore, the NDA is recommended for Approval.

B. Post Marketing (Phase 4) CMC-related Commitments, Agreements, and/or Risk Management Steps, if recommendation is for Approval
N/A.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Product(s)
Vidaza™ (azacitidine for injectable suspension) contains azacitidine, an analog of cytidine. Azacitidine differs from cytidine by having nitrogen in the 5 position of the heterocyclic ring. Azacitidine is 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one. The empirical formula of azacitidine is C₉H₁₂N₄O₅ and the molecular weight is 244. Azacitidine is manufactured for use in preparation of parenteral drug product, Azacitidine for Injectable Suspension.

Azacitidine is a white to off-white solid. Azacitidine was found insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

Vidaza should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. The vial should be inverted 2-3 times and gently rotated until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL.

The finished product is supplied in a sterile lyophilized form for reconstitution for subcutaneous injection only. Vials of Vidaza contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder. The supply is in single use vial
Executive Summary Section

The drug product is stored in unreconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F) (See USP Controlled Room Temperature). The proposed expiry dating period is 48 months.

B. Description of How the Drug Product is Intended to be Used
The recommended starting dose is 75 mg/m² subcutaneously daily for seven days, every four weeks. The dose may be increased to 100 mg/m² if no beneficial effect is seen after two treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 cycles. However, complete or partial response may require longer treatment. Treatment may be continued as long as the patient continues to benefit.

Preparation for Immediate Administration: Vidaza is reconstituted aseptically with 4 mL sterile water for injection. Doses greater than 4 mL should be divided equally into two syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into two syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2° C - 8°C, 36° F - 46° F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2-3 times and gently rolling the syringe between the palms for 30 seconds immediately prior to administration.

Vidaza is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas were the site is tender, bruised, red, or hard.

C. Basis for Recommended Action
NDA 50-794 is recommended for Approval from the CMC standardpoint based on the following:
- All CMC information is adequately provided and well studied.
- All facilities for manufacturing and controls of drug substance and drug product are found acceptable by the Office of Compliance.

III. Administrative

A. Reviewer’s Signature
Executive Summary Section

B. Endorsement Block

Li-Shan Hsieh/Date: Same date as draft review
Hasmukh Patel/Date
Amy Baird/Date

C. CC Block

APPEARS THIS WAY
ON ORIGINAL
Redacted 101

pages of trade secret and/or confidential commercial information
ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 50794/000

Action Goal:

Stamp: 29-DEC-2003

District Goal: 30-APR-2004

Regulatory Due: 29-JUN-2004

Brand Name: VIDAZA (AZACITIDINE INJEC)

Applicant: PHARMION

Estab. Name: TABLE SUSPENSION

IG 2525 28TH ST STE 2003

Generic Name: AZACITIDINE 100

BOULDER, CO 803012607

Priority: 1P

Dosage Form: (INJECTION)

Org Code: 150

Strength: 100 MG PER VIA

Application Comment: CHECK THESE FACILITIES ARE ADEQUATE OF THIS DRUG. (on 27-JAN-2004 by L. HSIEH (HFD-150) 30

-594-0497)

FDA Contacts:

Manager N. HEMINGWAY (HFC-41)

Chemist L. HSIEH (HFD-150) 301-594-0497 , Review

H. PATEL (HFD-810) 301-594-2570 , Team L

Overall Recommendation: ACCEPTABLE on 13-FEB-2004 by S. ADAMS (HFD-322) 30

-827-9051

Establishment: CFN

FEI

DMF No:

Responsibilities: AADA:
Profile: CSN

Estab. Comment: CHECK THIS FACILITY IS ADEQUATE OF DRUG SUBSTANCE (on 28-JAN-2004 by L. HSIEH (HFD-150) 301-94-0497)

Milestone Name

Creator

--------------- --------------- --------------- --------------- ---------------
SUBMITTED TO OC 28-JAN-2004 HSIEHL
SUBMITTED TO DO 28-JAN-2004 PS AMBROGIOJ
DO RECOMMENDATION 29-JAN-2004 MROBINSON
ACCEPTABLE BASED ON FILE REVIEW

GMP EI 3/13-4/1/2003 COVERED PROFILE CLASS CSN AND WAS
CLASSIFIED VAI AND PROFILED ACCEPTABLE. AN E-MAIL RESPONSE ON 1/29/04 FROM LI-SH N HSIEH,
REVIEW CHEMIST CONFIRMED THE FIRM WILL S CSN FOR

OC RECOMMENDATION 29-JAN-2004 ADAMS
ACCEPTABLE DISTRICT RECOMMENDATIO

Establishment: CFN 1519257 FEI 1519257
BEN VENUE LABORATORIES INC
270 AND 300 NORTHFIELD RD
BEDFORD, OH 441460568

DMF No: AADA:
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

SUBMITTED TO OC
HSIEHL
28-JAN-2004

OC RECOMMENDATION
AMBROGIOJ
28-JAN-2004
ACCEPTABLE
BASED ON PROFILE

Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CTL
OAI Status: NONE

Estab. Comment: CHECK THIS FACILITY IS ADEQUATE FOR
(on 28-
JAN-2004 by L. HSIEH (HFD-150) 301-594-0497)

Milestone Name
Creator

DATE TYPE Insp. Date Decision & Reason

SUBMITTED TO OC
HSIEHL
28-JAN-2004

SUBMITTED TO DO
AMBROGIOJ
28-JAN-2004 GMP

DO RECOMMENDATION
MPBEL
28-JAN-2004
ACCEPTABLE
BASED ON FILE REVIEW

PREVIOUS GMP EI OF 11/7/2001 WAS NAI
CHECK
WITH COMPLIANCE BRANCH REVEALED NO PENDING ENFORCEMENT ACTION THAT WOULD IMPACT THIS

RECOMMENDATION.

OC RECOMMENDATION 28-JAN-2004 ACCEPTABLE

AMBROGIOJ

DISTRICT RECOMMENDATIO

--------------------------

-------------

Establishment: CFN FEI

-------------

DMF No: AADA:

Responsibilities:

-------------

Profile: CTL OAI Status: NONE

-------------

EN 'estone Name Date Type Insp. Date Decision & Reason

-------------

SUBMITTED TO OC HSIEHL 28-JAN-2004

OC RECOMMENDATION 28-JAN-2004 ACCEPTABLE

AMBROGIOJ

BASED ON PROFILE

-------------
Methods validation not yet completed - see approval letter.

Appears this way on original.
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVL

OAI Status: NONE

Estab. Comment: CHECK THE FACILITY IS ADEQUATE

INJECTABLE PRODUCT. (on 28-JAN-2004 by L. HSIEH (HFD-150) 30-594-0497)

<table>
<thead>
<tr>
<th>Milestone Name</th>
<th>Date</th>
<th>Type</th>
<th>Insp. Date</th>
<th>Decision &amp; Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBMITTED TO OC HSIEHL</td>
<td>28-JAN-2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBMITTED TO DO AMBROGIOJ</td>
<td>28-JAN-2004</td>
<td>PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DO RECOMMENDATION Kculver</td>
<td>10-FEB-2004</td>
<td></td>
<td>ACCEPTABLE</td>
<td>BASED ON FILE REVIEW</td>
</tr>
</tbody>
</table>

C-9 DO RECOMMENDS APPROVAL FOR THIS FIRM'S ROLE IN THE NDA BASED ON FILE REVIEW AT REVIEW OF THE NDA.

OC RECOMMENDATION ADAMS | 13-FEB-2004 | ACCEPTABLE | DISTRICT RECOMMENDATION

---

Establishment: CFN FEI

DMF No: AADA:

Responsibilities: 

Profile: CTL OAI Status: NONE
HSIEH (HFD-150) 301-594-0497

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
<th>Type</th>
<th>Inspect Date</th>
<th>Decision &amp; Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBMITTED TO OC</td>
<td>28-JAN-2004</td>
<td></td>
<td></td>
<td>ACCEPTABLE</td>
</tr>
<tr>
<td>HSIEHL</td>
<td></td>
<td></td>
<td></td>
<td>BASED ON PROFILE</td>
</tr>
</tbody>
</table>

Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CTL

OAI Status: NONE

Estab. Comment: CHECK THIS FACILITY IS ADEQUATE

(on 28-JAN-2004 by L. HSIEH (HFD-150) 301-594-0497)