

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

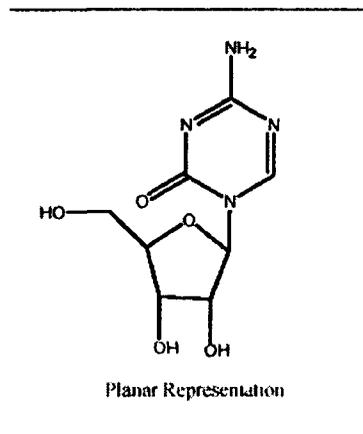
APPLICATION NUMBER

50-794

Chemistry Review(s)

NDA 50-794

Vidaza™
(Azacitidine for Injectable Suspension)



Pharmion Corporation

Li-Shan Hsieh, Ph. D.

**Division of Oncology Drug Products,
HFD-150**

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**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Review Data Sheet

1. NDA: 50794
2. REVIEW: 1
3. REVIEW DATE: 29-Apr-2004
4. REVIEWER: Li-Shan Hsieh, Ph. D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 64,251 N-015, (IC)	06-Jan-2003
IND 64,251 N-025 (IC)	23-Apr-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	26-Dec-2003
Amendment 002, BC	12-Mar-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Pharmion Coporation

Address: 2525 28th 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/TYPE:

- 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 FDCA (21 U.S.C. 360 cc)
 User Fee waiver: section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act.

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

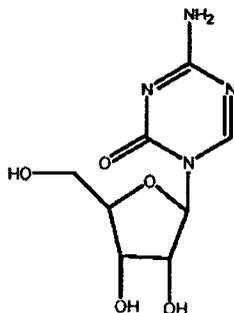
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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: C₈H₁₂N₄O₅, Relative Molecular Mass: 244.20



Planar Representation

17. RELATED/SUPPORTING DOCUMENTS:

IND 64,251 and IND 7574

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
-	IV	NCI	Clinical Information	7	N/A	N/A	No CMC information
-	V	Ben Venue Laboratories	\	1	Adequate	12-Mar-2004	Review by Dr. Marla Stevens-Riley
-	III	\	\	1	Adequate	02-Apr-2004	Reviewed by Dr. Hossein Khorshide
-	III	\	\	3	Adequate	05-Jul-2000	Reviewed by Dr. Chong-Ho Kim

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology (sterility assurance)	Approval	23-Apr-2004	Paul Stinavage, HFD-805
EES	Acceptable	13-Feb-2004	S. Adams, HFD-122
ODS	N/A		
LNC	N/A		
Pharm/Tox	Adequate	28-Apr-2004	Shwu-Luan Lee, HFD-150
Biopharm			Sophia Abraham, HFD-150

Methods Validation	N/A		
EA	Adequate	29-Apr-2004	Li-Shan Hsieh, HFD-150
Biostatistics (CMC statistics)	N/A		

**APPEARS THIS WAY
ON ORIGINAL**

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 C₈H₁₂N₄O₅ 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 where the site is tender, bruised, red, or hard.

C. Basis for Recommended Action

NDA 50-794 is recommended for **Approval** from the CMC standpoint 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

Profile: CSN OAI Status: NONE

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	Date	Type	Insp. Date	Decision & Reason

SUBMITTED TO OC
HSIEHL 28-JAN-2004

SUBMITTED TO DO
AMBROGIOJ 28-JAN-2004 PS

DO RECOMMENDATION
MROBINSO 29-JAN-2004 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
ADAMSS 29-JAN-2004 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 28-JAN-2004
HSIEHL

OC RECOMMENDATION 28-JAN-2004
AMBROGIOJ

ACCEPTABLE

BASED ON PROFILE

Establishment:

CFN

FEI

DMF No:

AADA:

Responsibilities:

Profile:

CTL

OAI Status:

NONE

Estab. Comment:
. (on 28-

CHECK THIS FACILITY IS ADEQUATE FOR

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
CAMPBELL

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
AMBROGIOJ

ACCEPTABLE

DISTRICT RECOMMENDATIO

Establishment: CFN
—
—
—
—

FEI —

DMF No: AADA:

Responsibilities: —
—

Profile: CTL OAI Status: NONE

EMilestone Name C. .tor	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC HSIEHL	28-JAN-2004			
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OC RECOMMENDATION AMBROGIOJ	28-JAN-2004			ACCEPTABLE
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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: CHECH THE FACILITY IS ADEQUATE

INJECTABLE PRODUCT. (on 28-JAN-2004 by L. HSIEH (HFD-150) 30
-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	PS		
DO RECOMMENDATION KCULVER	10-FEB-2004			ACCEPTABLE BASED ON FILE REVIEW
CFN-DO RECOMMENDS APPROVAL FOR THIS FIRM'S ROLE IN THE NDA BASED ON FILE REVIEW AL				
REVIEW OF THE NDA.				
OC RECOMMENDATION ADAMSS	13-FEB-2004			ACCEPTABLE DISTRICT RECOMMENDATIO

Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: CHECK THIS FACILITY IS ADEQUATE

(on 28-JAN-

:004 by L.

HSIEH (HFD-150) 301-594-0497)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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 (on 28-

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

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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