

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-273

CHEMISTRY REVIEW(S)

CMC REVIEW OF NDA 22-273

REVIEW # 1

**FLUDARABINE PHOSPHATE
TABLETS, 10 mg/Tab**

**JOSEPHINE M. JEE
CMC REVIEWER**

**OFFICE OF NEW DRUG QUALITY
ASSESSMENT
DIVISION OF PREMARKETING
ASSESSMENT AND
MANUFACTURING SCIENCE
(BRANCH V)**

**FOR THE DIVISION OF DRUG
ONCOLOGY PRODUCTS (HFD-150)**



CHEMISTRY REVIEW



NDA 22-273

Executive Summary Section FLUDARABINE PHOSPHATE TABLETS, 10 mg Table of Contents

Page 2 of 36 Pages

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability.....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and Drug Substance(s).....	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation	8
III. Administrative	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
S DRUG SUBSTANCE [Name, Manufacturer].....	9
P DRUG PRODUCT [Name, Dosage form]	13
A APPENDICES.....	17
R REGIONAL INFORMATION.....	17
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	17
A. Labeling & Package Insert.....	17
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	26
III. List Of Deficiencies To Be Communicated.....	26



CHEMISTRY REVIEW



NDA 22-273

Executive Summary Section
FLUDARABINE PHOSPHATE TABLETS, 10 mg

Page 3 of 36 Pages

Chemistry Review Data Sheet

1. NDA 22-273
2. REVIEW: # 1
3. REVIEW DATE: 25-JUL-2008
4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Fludarabine phosphate	
Pre-IND	30-JUL-2007
Pre-NDA CMC Mtg	None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 22-273	15-NOV-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Xanthus Pharmaceutical, Inc.*
Address: 300 Technology Square
Cambridge, MA 02139

* Xanthus was acquired by Antisoma on 20-JUN-2008. The address and telephone are retained.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Same as established name
b) Non-Proprietary Name (USAN): Fludarabine phosphate
International Nonproprietary Name (INN): Fludarabine phosphate
c) Code Name/# (ONDC only): NSC-312887
Internal Codes: ZK 153851
d) CAS Registry Number: 75607-67-9
e) CAS Name: 9H-purine-6-amine, 2-Fluoro-9-(5-O-phosphono-β-arabino furanosyl)-
e) Laboratory Codes: None provided.
f) Chemical Name (IUPAC): 2-Fluoro-9-(5-O-phosphono-β-arabino furanosyl)-9H-purine-6-amine
Alternative names: 2F-ara-AMP (Abbreviated Name)



CHEMISTRY REVIEW



NDA 22-273 FLUDARABINE PHOSPHATE TABLETS, 10 mg Page 4 of 36 Pages

- g) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 505(b)(2)
 - Submission Priority: S

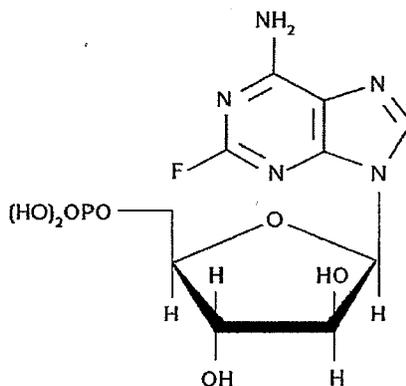
9. LEGAL BASIS FOR SUBMISSION:

FDC Act	505(b)(2)
RLD	Fludarabine Phosphate Tablets
Dosage Form	Tablets
Strength	10 mg/Tab
RLD	NDA 20-038
NDA Holder	Berlex Laboratories

NDA 22-273 was filed under section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

10. PHARMACOL. CATEGORY: Treatment of Adult Patient with B-cell Chronic Lymphocytic Leukemia (CLL)
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 10 mg/Tab
13. ROUTE OF ADMINISTRATION: Orally
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): N/A
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)-9H-purin-6- amine



Molecular Formula: C₁₀H₁₃FN₅O₇P

Molecular Weight: 365.2

**CHEMISTRY REVIEW**

NDA 22-273

Executive Summary Section
FLUDARABINE PHOSPHATE TABLETS, 10 mg

Page 5 of 36 Pages

17. RELATED/SUPPORTING DOCUMENTS:**A. DMFs:**

DMF #	T Y P E	HOLD ER	ITEM REFEREN CED	C O D E 1	STATUS 2	DATE REVIE W COMP LETED	COMME NTS
DMF 14924	I I	Bayer Schering Pharma	Fludarabine Phosphate	1	Adequate	08-JUL- 2008	Reviewed by J.Jee
DMF 20357	II	Bayer Schering Pharma	Fludarabine Phosphate Tablets	1	Adequate	22-JUL- 2002	Review conducted by J.Jee

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)**Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78,332	Fludarabine Phosphate
NDA	20-038	Fludarabine Phosphate Injection
DMF	14,924	Fludarabine Phosphate DS
DMF	20,357	Fludarabine Phosphate DP

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	31-JAN-2008	S.Adams	Acceptable on 10-JUL-2008
Pharm/Tox	Consult on Related substances..	20-JUN-2008	D.Y. Lee-Ham, Ph.D.	Acceptable on 20-JUN-2008
Biopharm	N/A	N/A	Gene M. William, Ph.D.	N/A
ODS/DMEPA	N/A			
Methods Validation	N/A			
EA	N/A	N/A	J.Jee	Categorical exclusion granted (see



CHEMISTRY REVIEW



Executive Summary Section

NDA 22-273

FLUDARABINE PHOSPHATE TABLETS, 10 mg

Page 6 of 36 Pages

				attached review).
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The Chemistry Review for NDA 22-273

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is approvable, pending the submission of acceptable container/carton labeling, including the Patient Information and Physician's Package Insert (see comments on page 36).

Note: The applicant name has changed on 20-JUN-2008 from Xanthus Pharmaceuticals, Inc. to Antisoma.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Fludarabine Phosphate Film-Coated Tablet is intended to treat adult patients with B-cell chronic lymphocyte leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent. Fludarabine Phosphate Tablets is available in 10 mg film-coated tablets. The tablet core contains 10 mg of fludarabine phosphate as the active pharmaceutical ingredient. Fludarabine Phosphate Film-Coated tablets are packaged in white plastic bottles that contain 15 or 20 tablets individually packaged in blister packs (5 tablets/blister strip, 3 or 4 blister strips/bottle). The plastic bottle is fitted with a child resistant cap and each individual bottle is contained in a white cardboard box dimensioned to the size of the bottle. The bottles and boxes will be labeled with approved labeling.

The drug product is an immediate release formulation containing pharmaceutical excipients that are conventional in nature and consists of microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silicon dioxide, croscarmellose sodium and magnesium stearate. The film-coat contains hypromellose, talc, titanium dioxide, and ferric oxide pigment (red/E172, yellow/E172). Fludarabine Phosphate Film-Coated Tablets are capsule shaped and salmon pink in color, marked on one side with "LN" in a regular hexagon. Fludarabine Phosphate Film-Coated Tablets are manufactured by Bayer Schering Pharma under DMF 20,357. An authorization letter from Bayer Schering Pharma dated 07-MAR-2007 is included in NDA 22-273.

Bayer Schering Pharma submitted batch analyses for _____ batches of fludarabine phosphate film-coated tablets ranging from over _____ tablets in size. Up to 36 months at 25°C/60% RH and 24 months at 30°C/70% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data were submitted for the _____ batches. The stability data obtained from all batches tested by Bayer Schering Pharma conform to the Fludarabine Phosphate Drug Product specification at 25°C/60% RH for up to 36 months, at 30°C/70% RH for up to 24 months storage. The proposed shelf-life of the tablets is 24 months at temperatures up to 30 °C. The stability data submitted support this proposed shelf-life.

b(4)



CHEMISTRY REVIEW



NDA 22-273

FLUDARABINE PHOSPHATE TABLETS, 10 mg

Page 7 of 36 Pages

Drug Substance:

Fludarabine phosphate is a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-beta - D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. Fludarabine phosphate is a white powder, soluble in water, freely soluble in dimethylformamide and practically insoluble in ethanol, methanol, and diethyl ether. Fludarabine phosphate is a USP compendial drug substance.

The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-β-D-arabinofuranosyl)(2-fluoro-ara-AMP). The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2).

The drug substance is manufactured, tested and packaged by Bayer Schering Pharma. The CMC information for fludarabine phosphate is found in DMF 14,924. An authorization from Bayer Schering Pharma dated 07-MAR-2007 is attached

b(4)

Fludarabine phosphate was accepted as a United States Adopted Name (USAN).

Bayer Schering Pharma submitted batch analyses for _____ commercial size _____ batches of fludarabine phosphate drug substance. Up to 48 months of long-term (6°C), 12 months at 25°C/60% RH and 30°C/70% RH, and 3 months at 40°C/75% RH stability data were submitted for _____ batches ranging from _____. The stability data obtained from all batches tested by Bayer Schering Pharma conform with the Fludarabine Phosphate Drug Substance specification at 6°C for up to 24 months, at 25 °C / 60 % RH for up to 3 months storage. Fludarabine phosphate failed to meet the specifications at 30°C/70% RH and 40°C/75% RH. The proposed storage conditions is at 6°C for 24 months.

b(4)

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

Fludarabine Phosphate Film-Coated Tablets would be supplied in white plastic bottles that contain 15 or 20 tablets individually packaged in blister packs (5 tablets/blister strip, 3 or 4 blister strips/bottle). The plastic bottle is fitted with a child resistant cap and each individual bottle is contained in a white cardboard box dimensioned to the size of the bottle. The bottles and boxes will be labeled with approved labeling.

Microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silicon dioxide, croscarmellose sodium and magnesium stearate and magnesium stearate are present as inactive ingredients in the tablet core (10 mg API). The film-coat contains hypromellose, talc, titanium dioxide, and ferric oxide pigment (red/E172, yellow/E172). Fludarabine Phosphate Film-Coated Tablets are capsule shaped and salmon pink in color, marked on one side with "LN" in a regular hexagon.

NDC XXXXX-1311-15: 15 -10 mg film-coated tablets per container. Each film-coated tablet is packaged in an individual blister package; 5 tablets per blister strip; 3 blister strips packaged in a plastic bottle with a child resistant container closure; each bottle is packaged in an individual chip-board.

NDC XXXXX-1311-20: 20 -10 mg film-coated tablets per container. Each film-coated tablet is packaged in an individual blister package; 5 tablets per blister strip; 4 blister strips packaged in a plastic bottle with a child resistant container closure; each bottle is packaged in an individual chip-board.

The recommended storage condition is at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].

The recommended handling and disposal statement is included in detail together with the applicable references.



CHEMISTRY REVIEW



Executive Summary Section

NDA 22-273

FLUDARABINE PHOSPHATE TABLETS, 10 mg

Page 8 of 36 Pages

The NDC numbers are pending. Applicant has changed from Xanthus Pharmaceuticals to Antisoma on 20-JUN-2008.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for Approvable from a Chemistry, Manufacturing, and Controls standpoint, pending the submission of acceptable container, carton and blister labeling including the Patient information and Physician's Package Insert. The establishment evaluation is acceptable on 10-JUL-2008 by the Office of Compliance.

III. Administrative

This NDA was submitted electronically with very limited information and in regular hard copy as a 505(b)(2) application. A Quality Overall Summary is not included in this application.

All pertinent information for fludarabine phosphate drug substance is adequately provided in DMF 14,924, Bayer Schering Pharma and DMF 20,357 for Fludarabine Phosphate Film-Coated Tablets, Bayer Schering Pharma.

Company name was changed on 20-JUN-2008 from Xanthus Pharmaceuticals, Inc. to Antisoma.

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

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28 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Josephine Jee
7/31/2008 11:11:19 AM
CHEMIST

Ravi Harapanhalli
7/31/2008 02:39:56 PM
CHEMIST

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22273/000

Sponsor: XANTHUS PHARM

Org Code : 150

300 TECHNOLOGY SQUARE

Priority : 5S

CAMBRIDGE, MA

Stamp Date : 19-NOV-2007
TABS FOR

Brand Name : FLUDARABINE PHOSPHATE

PDUFA Date : 19-SEP-2008

ORAL USE

Action Goal :

Estab. Name:

District Goal: 21-JUL-2008
TABS

Generic Name: FLUDARABINE PHOSPHATE

FOR ORAL USE

Dosage Form: (TABLET)

Strength : 10 MG

FDA Contacts: N. HEMINGWAY
-796-1365

Project Manager (HFD-120) 301

-796-1375 J. JEE

Review Chemist 301

-796-1747 H. SARKER

Team Leader (HFD-150) 301

Overall Recommendation: ACCEPTABLE on 10-JUL-2008 by S. FERGUSON (HFD-32)
2) 301-796-

3247

Establishment : CFN : 9610131

FEI : 3002808086

BAYER SCHERING PHARM AG

MULLERSTRASSE 170-178

BERLIN, , GM

b(4)

DMF No: 14924 20357

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Profile : _____ OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-JAN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Profile : _____ OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-JAN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

b(4)

Establishment : CFN : _____ FEI : _____

r

7

b(4)

L

J

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : _____ OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 15-APR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

b(4)

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

b(4)

DMF No:

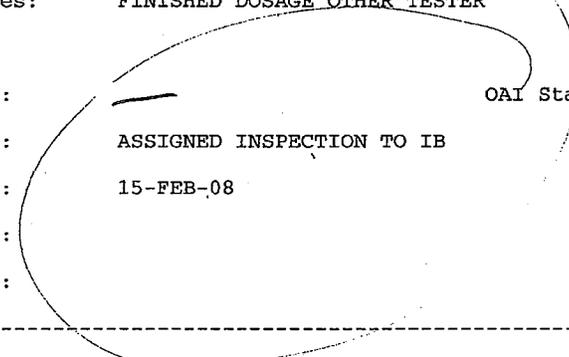
ADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : OAI Status: NONE

Last Milestone: ASSIGNED INSPECTION TO IB

Milestone Date: 15-FEB-08



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