CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

090724Orig1s006

Trade Name:	Fludarabine Phosphate
Generic or Proper Name:	Fludarabine Phosphate
Sponsor:	Areva Pharmaceuticals Inc.
Approval Date:	March 29, 2023
Indication:	Fludarabine Phosphate Injection is indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.

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090724Orig1s006

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Reviews / Information Included in this ANDA Review.

Approval Letter	**X**
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Summary Review	
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Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
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Pharm/Tox Review(s)	
Statistical Review(s)	
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Proprietary Name Review(s)	
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APPLICATION NUMBER:

090724Orig1s006

APPROVAL LETTER

ANDA 090724/S-006

PRIOR APPROVAL SUPPLEMENT
APPROVAL

Areva Pharmaceuticals Inc.
7112 Areva Drive NE
Georgetown, IN 47122
Attention: Victor Swami

Dear Mr. Swami:

This letter is in reference to your supplemental abbreviated new drug application (sANDA) received for review on January 3, 2023, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Fludarabine Phosphate Injection, USP, 25 mg/mL, 2 mL/vial.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The sANDA, submitted as “Prior Approval Supplement," provides for:

- Addition of (b) (4) as an alternate Drug substance manufacturer.

We have completed the review of this sANDA, as amended, and it is **approved**.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

If you have further questions regarding this supplement, you may contact LCDR Maria Clary, Pharm.D., Regulatory Business Process Manager, at (240) 402 - 8615.

Sincerely yours,

{See appended electronic signature page}

For:
Paul Schwartz, Ph.D.
Director, Division of Post Marketing Activities II
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Karen Bernard

Digitally signed by Karen Bernard
Date: 3/29/2023 11:43:31AM
GUID: 508da702000287e581cc3b10f0ce7fef

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

090724Orig1s006

CHEMISTRY REVIEW(S)

Disciplines Involved	Outcome		Disciplines Involved	Outcome
Chemistry	AC		Biopharmaceutics	NA
Microbiology	NA		Bioequivalence	NA
Facilities	AD		DMF (Chemistry)	AD
Labeling	NA		DMF (Microbiology)	NA
Submissions Assessed				
Received Date:	1/3/2023			
Amendment(s) Date:				

OFFICE OF PHARMACEUTICAL QUALITY
ASSESSMENT OF SUPPLEMENT TO ABBREVIATED NEW DRUG APPLICATION

Chemistry Assessment Number : 01

ANDA/Supplement Number : 090724/S-6

Drug Product Name, Strength : Fludarabine Phosphate Injection, USP, 25 mg/mL, 2 mL/vial

Pharmacological Category/ Indication(s) : Indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.

Applicant Name (or US Agent if Applicable) : Areva Pharmaceuticals (US agent NA)

Supplement Provides For : Addition of (b) (4) (b) (4) as an alternate Drug substance manufacturer.

Filing Category with basis for decision/comments (based on guidance for industry/CFR quotes) : PAS

Relevant Supporting DMF(s) Cited (If Applicable)

DMF No.	DMF	Result of Assessment	Date Assessment Completed
(b) (4)			

ASSESSMENT NOTES

This supplement is submitted by Areva Pharmaceuticals Inc hereafter known as applicant or firm with respect to its drug product, Fludarabine Phosphate Injection, USP; 25 mg/mL, 2 mL/vial proposing the addition of alternate API/DS source from (b) (4)

In addition to the above change, the applicant is also proposing the following annual reportable changes through this supplement; (b) (4)

Reviewer's comment: Satisfactory

Facility

The applicant is proposing a new DS supplier for its DP, Fludarabine Phosphate Injection, USP; 25 mg/mL, 2 mL/vial . The detail of the new proposed DS manufacturing site is provided below.

Product Name	DMF	DMF Holder & Address	FEI/ DUNS Numbers
Fludarabine Phosphate Injection, USP; 25 mg/mL, 2 mL/vial	(b) (4)		

Per FACTS Database, the proposed API supplier manufacturing site has satisfactory cGMP (Profile class codes: (b) (4) upon FDA inspection as of 08/24/2018 as seen below.

(b) (4)

The manufacturing facility has been approved as of 01/12/2023 within the scope of this PAS as seen below.

Submission Overall Manufacturing Facility Status

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	1/12/2023	Pending	ANDA-090724-SUPPL-6

A copy of corresponding LOA for DMF (b) (4) granting the applicant the rights to reference the DMF is provided in Module 1.4.1. Debarment certificate for (b) (4) is also provided in Module 1.3.3 and the cGMP certification and information on DS manufacturer are provided in Module 3.2.S.2.1.

Drug Substance

For the proposed alternate DS source, the specifications are established in accordance with the current USP monograph and the approved DS specification by the current API supplier (b) (4) There is no change in the specification comparatively except the (b) (4) as seen in the comparison table below. The table below summarizes a comparison between the USP monograph, current vendor COA and the proposed alternate API supplier COA

Drug Substance Comparison of (b) (4) with current USP monograph

Test	USP
Description	NA
(b) (4)	
Chromatographic Purity	TEST - A
	Iso-ara-guanine-monophosphate: NMT (b) (4)
	Isoguanine: NMT0.2%
	3,5-Diphosphate Analog: NMT (b) (4)
	Other Individual Impurity: NMT (b) (4)
	TEST - B
	2-Fluroadenine: NMT (b) (4)
	2-Fluro-ara-adenine: NMT (b) (4)
	2-Ethoxyphosphate Analog: NMT (b) (4)
	Other Individual Impurity: NMT (b) (4)
	Total Other Impurities: NMT (b) (4)
	Total Impurities: NMT (b) (4)
(b) (4)	

(b) (4)

(b) (4)

(b) (4)

The addition of (b) (4) *as an alternate Drug substance manufacturer is acceptable.* (b) (4)

RECOMMENDATION

☒ Supplement is CMC Approvable

☐ Supplement is NOT CMC Approvable (with brief explanation:)

(Choose ☐ IR, ☐ CR-Minor, ☐ CR-Major); Deficiencies noted below:

Deficiencies to be communicated: NA

Primary Assessor : Kevin Affram, Ph.D. **Date : March 28, 2023**

Kevin Affram

Digitally signed by Kevin Affram
Date: 3/28/2023 03:01:11PM
GUID: 5c0695140020e1a0237c75ad6058754b

Huiqi He

Digitally signed by Huiqi He
Date: 3/28/2023 03:44:21PM
GUID: 5449382100047e04e3dafc7da83252e5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

090724Orig1s006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/13/2023 06:43:15 AM
To: VSWAMI@AREVAPHARMA.COM
CC:
BCC:
Subject: INFORMATION REQUEST ANDA 90724/S-006

Good Afternoon,

Please see attachment and confirm receipt.

Respectfully,

LCDR Maria Antoinette Clary, Pharm.D.
Regulatory Business Process Manager
Division of Regulatory Business Process Management III
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food & Drug Administration
240-402-8615

Please find the attached documents below:

90724S6DP_IR.pdf

ANDA 090724/S-006

INFORMATION REQUEST

Areva Pharmaceuticals Inc.
7112 Areva Drive NE
Georgetown, IN 47122
Attention: Victor Swami

Dear Mr. Swami:

This letter is in reference to your supplemental abbreviated new drug application (sANDA) received for review on January 3, 2023, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Fludarabine Phosphate Injection USP, 25 mg/mL, 2 mL/vial.

We are reviewing the Quality section of your submission and have the following comments and information requests:

Drug Product

The Drug Master File holder was notified in regard to DMF (b) (4) Please consult with your DMF holder for pertinent information.

We request a prompt written response, no later than March 17, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact LCDR Maria Clary, Pharm.D., Regulatory Business Process Manager, at maria.clary@fda.hhs.gov or (240) 402 - 8615.

Sincerely,

{See appended electronic signature page}

LCDR Maria Clary, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Maria Clary

Digitally signed by Maria Clary
Date: 3/13/2023 06:40:44AM
GUID: 525816760002eaa7fe6a779099a46872

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/19/2023 12:24:53 PM
To: VSWAMI@AREVAPHARMA.COM
CC:
BCC:
Subject: ANDA 90724/S-006

Good Afternoon,

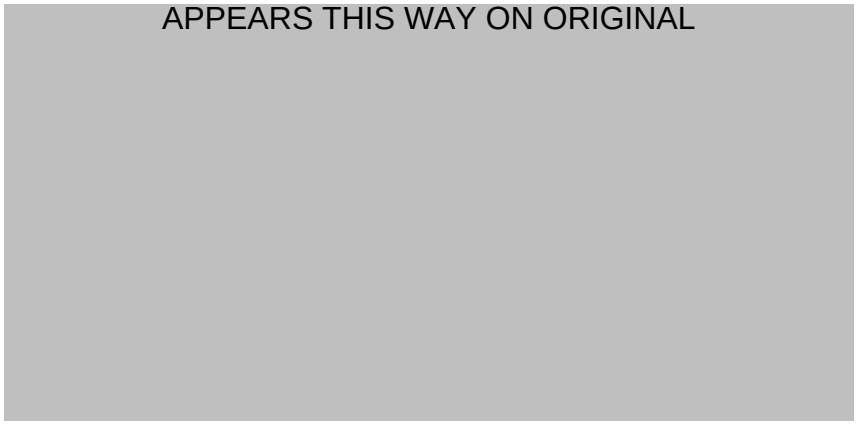
Please see attachment and confirm receipt.

Sincerely,

LCDR Maria A. Clary, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Please find the attached documents below:

90724 006 ACK.pdf



ANDA 090724/S-006

ACKNOWLEDGEMENT
PRIOR APPROVAL SUPPLEMENT

Areva Pharmaceuticals Inc.
7112 Areva Drive NE
Georgetown, IN 47122
Attention: Victor Swami

Dear Victor Swami:

This is in reference to your supplemental abbreviated new drug application (sANDA) received on January 3, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Fludarabine Phosphate Injection USP, 25 mg/mL, 2 mL/vial.

This prior approval supplement is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). This submission meets the criteria listed in section 505(j)(11) of the FD&C Act or the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* If FDA determines that an inspection or the use of a time- and resource-intensive alternate facility assessment tool is not required to validate the information contained in this priority supplement, the GDUFA goal date for review of this priority supplement is May 3, 2023. If FDA determines that an inspection or the use of a time- and resource-intensive alternate facility assessment tool is required to validate the information contained in this priority supplement and a Pre-Submission Facility Correspondence was not submitted or was found to be incomplete or inaccurate, the GDUFA goal date for review of this priority supplement is November 3, 2023. Multiple goal dates are provided because FDA is unable to determine if a supplement requires an inspection or the use of a time- and resource-intensive alternate facility assessment tool at the time of submission. FDA will make this determination during the assessment of the supplement. For information, see FDA's guidance for industry, *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA*.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that

occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

For additional information about supplements, please refer to the guidance for industry, *ANDA Submissions – Prior Approval Supplements Under GDUFA* available on FDA's website[1].

As described in the draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact LCDR Maria Clary, Pharm.D., Regulatory Business Process Manager, at maria.clary@fda.hhs.gov[2] or (240) 402 - 8615. Sign up for Generic Drug e-mail updates[3], which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

LCDR Maria Clary, Pharm.D.
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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1 We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

2 A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

3 See FDA's Subscription Management Center at https://www.fda.gov/about-fda/contact-fda/get-email-updates

Maria Clary

Digitally signed by Maria Clary
Date: 1/19/2023 12:23:33PM
GUID: 525816760002eaa7fe6a779099a46872