Project Renewal Assessment Aid

NDA 022137

Fludarabine Phosphate Injection 25 mg/mL (50 mg/2 mL)

Version date: September 2021 (ONLY for Project Renewal sNDA reviews)

Disclaimer: The FDA's recommendations and opinions are limited to this Assessment Aid and do not extend to other documents regarding this application. In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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1.0 EXECUTIVE SUMMARY

1.1. Product Introduction and Relevant U.S. Regulatory History

Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL) is a nucleotide metabolic inhibitor that was approved on September 21, 2007, under New Drug Application (NDA) 022137. NDA 022137 is a 505(b)(2) application that relied for approval on FDA's finding of safety and effectiveness for Fludara (fludarabine phosphate) (NDA 020038), which was originally approved in 1991. Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL) was initially approved 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.

On February 18, 2011, a prior approval supplement was approved that provided for revisions to the prescribing information to make it consistent with the relied-upon listed drug, Fludara. The following sections of the prescribing information were revised: Boxed Warning; Section 5, Warnings and Precautions; Section 6, Adverse Reactions; Section 11, Description; and Section 16, How Supplied/Storage and Handling. The NDA for Fludara was withdrawn in 2013, not for reasons of safety or effectiveness.

This Project Renewal Assessment Aid for Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL), (NDA 022137) provides a summary of the key proposed FDA recommendations for updates to the information related to approved uses for Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL) to align with 21 CFR 201.56 and 201.57 and applicable guidances,[1] as well as proposed recommendations for adding or modifying an indication(s) or other conditions(s) of use based on certain data and information, including published literature, FDA's finding of safety and effectiveness of listed drug(s), and/or information to which the Applicant would need to obtain a right of reference.

In addition, the FDA's independent assessment to support proposed recommendations for labeling modifications included published literature review, FDA Adverse Event Reporting System data, and assessment of the existing Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL) labeling. FDA's key proposed recommended labeling modifications are described below. Rationale for additional proposed labeling updates are provided in annotated comments to the Applicant, including references where appropriate, within the proposed draft labeling.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Refer to Section 12 References for the list of applicable guidances.

1.2. Information to Support the Proposed Changes to Labeling

The published literature cited in the annotated labeling support the FDA's proposed updates to the Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL) product labeling. The Applicant should submit any additional data or information relevant to the labeling updates proposed in the above-reference supplement(s). We note that NDA 022137 is a 505(b)(2) application that relies on the Agency's finding of safety and effectiveness for Fludara (NDA 020038). Generally, a supplement to an approved 505(b)(2) application is considered a 505(b)(2) supplement because the applicant continues to rely upon the basis for the Agency's previous finding of safety and effectiveness for the 505(b)(2) application for approval of the supplement. Further, because some of the evidence supporting the labeling updates may be derived from information the Applicant does not own or for which the applicant does not have a right of reference, the Applicant must submit the supplement pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

Based on the evaluation of information identified through this process and as further assessed by the FDA in conjunction with a review of additional published literature (as annotated in the proposed labeling), the following key labeling modifications, including new indications or modifications to existing indications and to dosage and administration, are proposed for inclusion in the Fludarabine Phosphate Injection 25 mg/mL (50 mg/2mL) labeling.

Any additional new indication(s) that the Applicant would like to propose that are not reflected in this Assessment Aid are outside the scope of Project Renewal and should be discussed individually with the appropriate FDA oncology review division.

2.0 PROPOSED REVISIONS TO INDICATIONS AND DOSAGE AND ADMINISTRATION

2.1. B-cell Chronic Lymphocytic Leukemia (CLL)

Summary of Proposed Changes

- The pre-existing indication of single agent Fludarabine Phosphate Injection is 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. The safety and effectiveness of Fludarabine Phosphate Injection in previously untreated or nonrefractory patients with CLL have not been established." The indication statement has been modified to remove "patients" as a descriptor of the term "adults" and to remove "standard" as a descriptor for the alkylating-agent containing regimen.
- The statement "The safety and effectiveness of Fludarabine Phosphate Injection in previously untreated or non-refractory patients with CLL have not been established" has been removed due to more recent safety and effectiveness data that is used to support modification of the indication statement.
- The indication for CLL has been expanded to include use as a component of a combination regimen for the treatment of adults with B-cell CLL irrespective of prior therapies received.
- The Recommended Dosage of Fludarabine Phosphate Injection has been modified to add the recommended dosage of Fludarabine Phosphate Injection for use in combination with cyclophosphamide and rituximab.
- The Recommended Dosage of Fludarabine Phosphate Injection when used as a single agent has been modified to remove general information and advice relating to potential toxicities associated with Fludarabine Phosphate Injection, as it is not typically included in Section 2 of labeling.

Indications and Usage

Section 1: B-cell Chronic Lymphocytic Leukemia

Fludarabine Phosphate Injection is indicated:

- as a component of a combination regimen for the treatment of adults with B-cell chronic lymphocytic leukemia (CLL);
- for the treatment of adults with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one alkylating-agent containing regimen.

Dosage and Administration

Section 2.1: Recommended Dosage for B-Cell Chronic Lymphocytic Leukemia (CLL)

In Combination with Cyclophosphamide and Rituximab
The recommended dosage of Fludarabine Phosphate Injection is 25 mg/m^2 administered intravenously over 30 minutes daily for the first three days (Days 1 to 3) of each 28-day cycle for 6 cycles or until unacceptable toxicity or disease progression, in combination with cyclophosphamide 250 mg/m^2 administered intravenously daily for three days (Days 1 to 3), and rituximab 375 mg/m^2 administered intravenously on Day 1 of the first cycle, followed by 500 mg/m^2 on Day 1 of subsequent cycles.

Refer to the cyclophosphamide and rituximab prescribing information for additional dosing information as appropriate.

Single Agent
The recommended dosage of Fludarabine Phosphate Injection is 25 mg/m^2 administered intravenously over 30 minutes daily for five consecutive days (Days 1 to 5) of each 28-day cycle.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• B-cell chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disorder (lymphoid neoplasm) that constitutes 1.1% of all new cancer diagnoses with an estimated 21,250 new cases diagnosed in 2021 (American Cancer Society, 2021). • CLL is a heterogenous disease with certain subsets of patients having survival rates without treatment that are similar to the general population. • CLL mainly affects older adults and the average age of diagnosis is 70 years.	B-cell CLL is a rare but serious and life-threatening condition that is primarily diagnosed in older adults.
Current Treatment Options	• Treatment of CLL depends on several factors, including patient comorbidities, age, stage, and presence or absence of symptoms. • Some patients (i.e., early stage asymptomatic) may be observed	There are several available therapies for use in patients with CLL that require treatment. The optimal treatment regimen in the first or subsequent lines has

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	initially rather than requiring immediate treatment. • Patients with active disease (those who develop disease-related symptoms or evidence of progressive disease) or patients with more advanced stage CLL may require treatment to improve symptoms and prolong progression-free and overall survival. • Fludarabine was initially approved in 1991 as a single agent for the treatment of patients with CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. • Several therapies exist for the treatment of patients with CLL, including Bruton tyrosine kinase inhibitors, BCL2 inhibitors, monocloncal antibodies, purine analogs, and alkylating agents.	not been established. Fludarabine as a single agent and in combination with other drugs has been used to treatment CLL for several years. CLL remains incurable with available therapy and new treatment options are needed.
Benefit	• Fludarabine as a single agent was approved on the basis of two single-arm studies in adult patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. In a study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were treated with a dose of 22 to 40 mg/m2 daily for 5 days every 28 days. Another study conducted by the Southwest Oncology Group (SWOG) involved 31 patients treated with a dose of 15 to 25 mg/m2 daily for 5 days every 28 days. The overall response rates (ORR) were 48% and 32%, respectively and the complete response (CR) rate was 13% in both studies. The median survival of all refractory CLL patients was 43 weeks and 52 weeks in	Fludarabine as a single agent was approved in 1991 for patients with CLL refractory to at least one prior standard alkylating-gent containing regimen. Fludarabine in combination with cyclophosphamide and rituximab has been evaluated in patients with CLL who are treatment naïve and also in patients who have progressed on prior therapy. In both patient populations, FCR improved PFS compared to a prior standard therapy, FC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the MDAH and SWOG studies, respectively (Fludarabine Phosphate U.S. Prescribing Information). • Eichhorst (2006) and Flinn (2007) were both prospective, randomized, phase III trials in patients with previously untreated CLL who were randomized to either fludarabine alone or fludarabine + cyclophosphamide (FC). Both studies demonstrated that the combination led to higher rates of response, CR, and progression-free survival (PFS) when compared to fludarabine alone. • Wierda (2005) was a single arm trial in 177 patients with previously treated CLL who received fludrabine, cyclophosphamide, and rituximab (FCR). CR was achieved in 25% of patients and the ORR was 73%. • Robak (2010) was a prospective, randomized, phase III trial of FC vs. FCR in patients with previously treated CLL. Patients on both arms received fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day for 3 days repeated every 28 days for up to 6 cycles. Patients randomly assigned to the FCR arm also received rituximab 375 mg/m^2 by IV infusion on day 1 of the first cycle and then 500 mg/m^2 IV on day 1 of subsequent cycles. The primary endpoint was PFS. FCR demonstrated a statistically significant improvement in PFS vs. FC (HR 0.65; $p<0.001$; median PFS 31 months vs. 21 months). • Hallak (2010) was a prospective, randomized, phase III trial of FC vs. FCR in patients with treatment-naïve CLL. All patients received fludarabine	Rituximab is approved in combination with fludarabine and cyclophosphamide for patients with CLL, the same combination regimen that is being proposed under Project Renewal. The measures of efficacy (e.g., median PFS, hazard ratios for PFS) in the rituximab USPI differ from those denoted in this assessment of fludarabine. The FDA review team notes that the differences in reported medians and HR for PFS cited in the rituximab USPI and those in this review are due to differences in the timing of interim analyses cited to support these respective applications. Additionally, the approval of rituximab included primary data review while the review of fludarabine is based on published literature. There may be differences in reported measures of efficacy based on differences in review methodologies, however, both methods reliably conclude the benefit of FCR for the proposed indication. In patients with CLL,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	25 mg/m^2 per day and cyclophosphamide 250 mg/m^2 per day for the first 3 days of each 28-day cycle for 6 cycles. Patients assigned to the FCR arm also received rituximab at a dose of 375 mg/m^2 on day 0 of the first cycle and 500 mg/m^2 on day 1 of the second to 6^{th} cycles. The primary endpoint was PFS. At 3 years after randomization, 65% of patients in the FCR group were free of progression compared with 45% in the FC group (HR 0.56 [95% CI: 0.46, 0.69), $p<0.0001$). In the FCR group, 87% were alive vs. 83% in the FC group (HR 0.67 (95% CI: 0.48, 0.92); $p=0.01$).	prolonging PFS can be clinically meaningful because progression is associated with symptoms of the disease that affect patients' quality of life. Obtaining a response to FCR may also lead to a treatment-free period for patients, which can benefit patients' quality of life.
Risk and Risk Management	• In the Robak 2010 study, rates of adverse events, Grade 3 or 4 events, and serious adverse events were higher in the FCR arm than the FC arm but no new safety signals were identified. • In the Hallek 2010 study, more patients had grade 3 and 4 neutropenia and leukocytopenia in the FCR arm but the rate of severe infections was not increased. No new safety signals were identified.	FCR may cause myelosuppression, infections, or other adverse events. In clinical studies of FCR, 35% of patients were 65 years and older. The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving FCR who were 70 years and older compared to younger patients for neutropenia, febrile neutropenia, anemia, thrombocytopenia, pancytopenia, and infections.

The Applicant's Position

The Applicant Agrees

The FDA's Assessment

The FDA agrees with the Applicant's position.

The existing indication for Fludarabine Phosphate Injection as single-agent therapy was updated, with “adult patients” changed to “adults” and the word “standard” removed.

A new indication for Fludarabine Phosphate Injection as part of a combination regimen has been added. The efficacy of Fludarabine Phosphate Injection for treatment of adults with B-cell CLL as a component of a combination regimen was derived from studies of fludarabine phosphate in the published literature. Fludarabine phosphate as a component of a combination regimen was evaluated in two randomized clinical trials (NCT00090051 and NCT00281918). In both trials, the major efficacy outcome measure was progression-free survival.

3.0 NONCLINICAL PHARMACOLOGY/TOXICOLOGY PERTINENT TO PROPOSED UPDATED LABELING

Fludarabine Phosphate Injection is a nucleotide metabolic inhibitor. Nonclinical pharmacology and toxicology information was revised; refer to sections 8, 12.1, 13, and subsections of 5 and 17 of the proposed annotated product labeling for rationale and references, where applicable.

- Section 8.1, Pregnancy modified to align with current labeling practice and to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and align with current labeling practice and guidance. The Applicant will be asked by FDA to review and summarize any other information on pregnancy, lactation, or reproductive potential, if available.
- Prior Section 8.3, Nursing Mothers, modified to new 8.2, Lactation Risk Summary. It appears there are no data on the presence of fludarabine phosphate or its metabolites in human milk, the effects of the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with Fludarabine Phosphate Injection, and for 1 week after the last dose.
- New Section 8.3, Females and Males of Productive Potential added to align with current FDA labeling practices.
- Section 12.1, Mechanism of Action, revised to provide what is known about the drug's established mechanism(s) of action (MOA).

The Applicant's Position

The Applicant Agrees

The FDA's Assessment

The FDA agrees with the Applicant's position. The Applicant accepted the FDA's proposed revisions to sections 8, 12.1, 13, and subsections of 5 and 17 of the product labeling.

In addition, the FDA reviewed the Established Pharmacologic Class (EPC) text phrase in the highlights section. The FDA proposed the EPC text phrase be revised from "nucleotide metabolic inhibitor" to "nucleoside metabolic inhibitor"; the Applicant accepted the FDA's proposal.

No new nonclinical information or reference to published literature is needed to support the product labeling revisions described above.

4.0 CLINICAL PHARMACOLOGY PERTINENT TO PROPOSED UPDATED LABELING

Clinical pharmacology information in the proposed annotated labeling Sections 2.2, 7.1, 8.4, 8.6, 12.2, and 12.3 were revised to align with the recommendations described in the FDA Guidance on Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance. The proposed clinical pharmacology-related changes and supporting published references are provided in the annotated labeling. The following changes were proposed:

- Section 2.2, Dosage Modifications for Renal Impairment, revised format for consistency with current labeling practice.
- Section 7.1, Drug Interactions with Pentostatin revised to state that the risk of pulmonary toxicity is severe.
- Section 8.4, Pediatric Use, revised to state that the safety and effectiveness have not been established in pediatric patients 1 years to < 17 years with refractory acute leukemia or solid tumors. The Applicant was advised to only include information on pediatrics defined as < 17 years.
- Section 8.6, Renal Impairment, revised format for consistency with current labelling practice.
- Section 12.2, Pharmacodynamics, revised to add the required statements regarding exposure-response relationships and relationship between higher fludarabine exposures and adverse reactions (if available). The Applicant was advised that if this information is not available or well characterized, then the proposed statement shown in the draft labeling should be utilized.
- Section 12.3, Pharmacokinetics, revised format for consistency with current labeling practice. The Applicant is advised to add a description of the metabolism of fludarabine under the heading provided, with information source if applicable.

The Applicant's Position

The Applicant Agrees

The FDA's Assessment

Section 7.1 has been revised to state that use of fludarabine should be avoided in combination with pentostatin due to the risk of severe and fatal pulmonary toxicity. The revision is acceptable.

Section 8.4 has been revised to define pediatrics as < 17 years. No new data or claims pertaining to clinical pharmacology in pediatric patients were included.

Section 12.2 has been revised to state that the exposure-response and pharmacodynamic response of fludarabine have not been characterized, which is acceptable.

The format revisions to Section 2.2 and 12.3 are acceptable.

The proposed expanded indication includes the use of fludarabine in combination with rituximab and cyclophosphamide in patients with CLL. The proposed fludarabine dosage of 25 mg/m^2 on the first three days of each 28-day cycle in combination with cyclophosphamide 250 mg/m^2 and rituximab 375/500 mg/m^2 is supported by the results from existing studies described in Robak 2010 and Hallek 2010. The proposed dosage is acceptable based on clinical review team's assessment. Refer to FDA assessment to Section 2.1 for detailed information.

5.0 SAFETY PERTINENT TO PROPOSED UPDATED LABELING

Existing safety data were reviewed and any proposed safety-related changes and supporting published literature are provided in the proposed annotated labeling.

Substantive proposed changes to the safety sections of the Fludarabine Phosphate labeling include the following:

- The boxed warning for severe bone marrow suppression, CNS toxicity, hemolytic anemia, and pulmonary toxicity was removed. This information has been moved and managed using the Warnings and Precautions section to align with the recommendations described in FDA's Guidance: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format, and to be more consistent with other current product labeling.
- Section 2.2, Dose Modifications for Renal Impairment modified. Dose modifications for renal impairment stated "do not administer." This was changed to "A reduced dose has not been established." Guidelines dosage for Creatinine Clearance >80 ml/min removed, as this is not considered renal impairment.
- Warnings and Precautions have been modified:
    - "Dose dependent neurologic toxicities" has been modified to "Neurologic Toxicities." Language regarding several, irreversible CNS effects that have been noted to occur at doses approximately 4 times great than the recommended dose for fludarabine have been moved to Section 10: Overdosage. Other changes include contemporary language consistent with current FDA practice, including monitoring patients for signs and symptoms of this toxicity.
    - "Bone marrow suppression" has been modified to "myelosuppression." Language has been updated to include contemporary language consistent with current FDA practice and to align with more recent approvals for related products with dose-limiting myelosuppression.
    - "Autoimmune reactions" has been modified to "autoimmune cytopenias." Statements regarding discontinuation of therapy due to this event has been removed to defer to the practice of medicine since there are now available therapies that may be used to manage patients who develop autoimmune cytopenias.
    - "Pregnancy" has been removed as a warning and precaution and this information has been moved down to Section 8 to reflect the relative clinical significance of the adverse reactions to the indicated population and to be consistent with FDA current best labeling practices.
    - "Male fertility and reproductive outcomes" has been removed as a warning and precaution and has been moved to Section 8.3, in accordance with the PLLR and relevant labeling guidance, as well as to be consistent with other related oncology products.

    - "Tumor lysis syndrome" is maintained but language has been adjusted to be consistent with current FDA best labeling practices.
    - "Pulmonary Toxicity" section updated to clarify this event occurs in combination with pentostatin more clearly.
    - "Renal Impairment" has been removed as a warning and precaution because this section does not currently describe information related to serious adverse reactions in patients with renal impairment treated with fludarabine. FDA believes that adequate directions for safe use have been provided in Section 2.2 and 8.6 to manage required dose modifications for renal impairment.
    - "Embryo-fetal toxicity" has been revised to align with PLLR and applicable guidance, as well as FDA current labeling practices.
- Section 6: Adverse Reactions has been modified
    - Information listed under Section 6 has been reorganized under the numerical subsections 6.1 Clinical Trials Experience and 6.2 Postmarketing Experience in accordance with the FDA guidance for the adverse reactions section of labeling. Adverse reactions listed in 6.1-6.11 were not repeated in 6.2 to be as concise as possible.
    - The common adverse reactions statement was revised to use pooled incidence from the MDAH and SWOG trials based on information provided in Table 2 and to align with FDA guidance and OCE/OOD best labeling practices.
    - The AR incidence cutpoint was added to be consistent with FDA Guidance. The incidence rate of ≥20% was used based on comparable product labeling.
    - The table summarizing patients reporting non-hematologic adverse reactions was revised to provide a frequency cutoff of ≥5% in patients treated with fludarabine in the MDAH or SWOG trials for brevity and to better align with the FDA guidance for the adverse reactions section of labeling. Adverse reactions occurring at <5% that were removed from the common adverse reactions table are now listed below the table in text under updated SOC terms. The table was reordered to provide the adverse reactions in decreasing order of frequency to confirm with current guidance.
    - The hematologic adverse reaction information previously in Section 6.1, Hematopoetic Systems, was moved in front of the common adverse reactions table since these are the most common adverse reactions. Since the incidence rates for each of these adverse reactions are not available for each term, they were not incorporated into Table 2 for this labeling.
    - Section 6.2 Postmarketing experience was populated using statements that identified postmarketing adverse reactions in previous fludarabine labeling. Adverse reactions that were previously identified in 6.1 Clinical Trials Experience were removed and not repeated in this section for brevity and based on OCE/OOD best labeling practices.

- Geriatric Use
    - This section was updated based on differences observed between older and younger patients.

The Applicant's Position

The Applicant Agrees

The FDA's Assessment

The FDA agrees with the Applicant's position. The Applicant has made the revisions specified above as outlined.

6.0 PEDIATRIC INFORMATION PERTINENT TO PROPOSED UPDATED LABELING

Pediatric information was reviewed; proposed changes related to pediatric information and supporting published literature are discussed in the pediatric sections in the proposed annotated labeling, including section 8.4 and other sections, where applicable.

Substantive proposed changes to the pediatric sections of the FDA product label include:

- Section 8.4, Pediatric Use, revised to align with the recommendations described in the FDA Guidance: Pediatric Information Incorporated into Product Labeling and current oncology best labeling practices.
- Information on use of Fludarabine Phosphate was deleted because this information did not show differences between pediatric patients and adults and therefore was not necessary.
- Information on dosing was removed because dosing regimens must not be implied or suggested in other sections of the labeling if not included in Indications and Usage [21 CFR 201.57(c)(3)(ii)].

The Applicant's Position

The Applicant Agrees

The FDA's Assessment

The FDA agrees with the Applicant's position. The Applicant has revised the USPI as outlined above. The Applicant confirmed that they have not conducted any clinical study to support pediatric use, therefore no further pediatric data were included in Section 8.4, Pediatric Use.

7.0 ADDITIONAL PROPOSED LABELING CONSIDERATIONS

Full Prescribing Information: Following review of the existing product labeling, and independent FDA review of available evidence, FDA included additional proposed modifications in the proposed annotated product labeling attached to the Supplement Request Letter for consistency with FDA labeling regulations and to more closely align with guidance.

Where applicable, format and content of the labeling were updated to conform to the Physician Labeling Rule (PLR) and align with current labeling guidances.

HIGHLIGHTS

- The Applicant should update the highlights to reflect final labeling proposal.

TABLE OF CONTENTS

- The Applicant should update the table of contents to reflect final labeling proposal

Section 2

- Section 2.5, "Use of Infusion Solutions" modified to "Preparation and Administration". Language updated to note that Fludarabine Phosphate is a hazardous drug and should follow applicable special handling and disposal procedures. Other editorial changes made in this section to align with FDA best labeling practices.

Section 3

- Section 3, Dosage Forms and Strengths modified and requests made to Applicant to complete further information. Drug products containing an active ingredient that is a salt should clearly state the product contents in a manner that allows the reader to understand whether the strength is based on the active moiety or active ingredient (salt). Reference to FDA Guidance: Naming of Drug Products Containing Salt Drug Substances (III.B) provided to Applicant. If the appearance of a parenteral dosage form (e.g., injection, for injection) is visible to the health care practitioner, the Applicant should include identifying characteristics including information about color (e.g., colorless to slightly pale-yellow solution) and clarity (e.g., clear to slightly cloudy). Request for revision to this information to include applicable color and clarity for Fludarabine Phosphate Injection.

Section 4

- No revisions made.

Section 5

- Revisions made throughout. See Section 5 of this review, entitled "Safety Pertinent to Proposed Updated Labeling."

Section 6

- Revisions made throughout. See Section 5 of this review, entitled "Safety Pertinent to Proposed Updated Labeling."

Section 8

- Revisions made include:
    a. Update to Section 8.1, Pregnancy; Section 8.2, Lactation, Section 8.3 Females and Males of Reproductive Potential. See Section 3.0 of this review, entitled “Nonclinical Pharmacology/Toxicology Pertinent to Proposed Updated Labeling” for a summary of these changes.
    b. Section 8.4, Pediatric Use, revised to be consistent with the FDA Guidance: Pediatric Information Incorporated into Product Labeling and current oncology best labeling practices. See Section 6.0 of this review for further information.
    c. Section 8.5, Geriatric Use, revised to include pertinent efficacy and safety difference in patients by age observed in clinical trials supporting fludarabine phosphate’s use.
    d. Section 8.6, Renal Impairment, revised to align with current FDA labeling practices.

Section 10

- Section 10, Overdosage, revised to include information on severe, irreversible CNS effects that can occur with Fludarabine overdose based on information previously in Section 5.

Section 11

- Section 11, Description, revised to the Established Pharmacologic Class (EPC) text phrase listed for fludarabine to “nucleoside metabolic inhibitor” (vs. the currently labeled “nucleotide metabolic inhibitor”. Information regarding resistance to deamination by adenoside deaminase also removed, as this information is not relevant to healthcare practitioners and it appears that vidarabine has been withdrawn from the market.

Section 14

- Section 14 B-cell Chronic Lymphocytic Leukemia section revised to be consistent with current FDA labeling practices (i.e., adding qualifiers to the recommended dosage to avoid suggesting or implying dosing regimens note stated in Section 2 of the labeling).
- New subsection under 14 In Combination with Cyclophosphamide and Rituximab, added to summarize efficacy findings from 2 randomized clinical trials that support the indication and dosage revisions in Sections 1 and 2 of labeling.

Section 16

- Section 16, How Supplied/Storage and Handling revised to be consistent with current FDA guidance.

Section 17

- Section 17, Patient Counseling Information, revised to confirm with current FDA guidance on Patient Counseling Section of Labeling.

Package and Container Labeling: The Applicant should submit copies of all container/carton labeling with any necessary updates to ensure adherence to current regulations and guidance.

The Applicant's Position

The Applicant Agrees

The FDA's Assessment

The FDA agrees with the Applicant's position. The Applicant has revised the USPI and the container/carton labeling as outlined above.

8.0 FDA'S RECOMMENDATIONS

8.1. Clinical

The FDA review team recommends approval.

8.2. Non-Clinical

The FDA review team recommends approval.

8.3. Clinical Pharmacology

The FDA review team recommends approval.

8.4. Quality

The FDA review team recommends approval.

9.0 FDA REVIEW TEAM SIGNATURE PAGE

X X

Primary Quality Reviewer | Team Lead

X X

Primary Pharm/Tox Reviewer | Pharm/Tox Team Lead

X X

Primary Clinical Pharmacology Reviewer | Clinical Pharmacology Team Lead

X X

Primary Clinical Reviewer | Clinical Team Lead

X

Associate Director for Labeling

X X

Safety Evaluator (OOD-Safety Team)

Disclaimer: The FDA's recommendations and opinions are limited to this Assessment Aid and do not extend to other documents regarding this application. In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

10.0 OFFICE DIRECTOR

X

Office Director (or designated signatory authority)

11.0 APPENDICES

See annotated package insert containing FDA's recommended updates**.**

11.1. Sources of Clinical Data and Review Strategy

The Project Renewal Support Team reviewed information regarding potential unapproved uses in the post-marketing setting as described in multiple drug compendia.[2] Following identification of potential labeling changes regarding new/updated indications and dosage regimens, the Project Renewal Support Team obtained agreement from the new drug application holder for participation in this process. The Project Renewal Support Team then identified Research Team Members (RTMs), defined as subject matter experts and key opinion leaders with expertise in these disease areas based on recommendations by relevant professional organizations.[3] Medical hematology/oncology fellows were also included as part of the educational component of this project; both RTMs and hematology/oncology fellows evaluated scientific literature identified through a python-based tool of PubMed describing such unapproved uses, including both positive and negative studies.

Research teams were formed with relevant disease-specific expertise; the teams discussed the available data in a series of meetings to reach consensus regarding proposals for labeling modifications. Specifically, the teams considered existing labeling including dose, safety, pharmacology and special populations, and whether there were adequate data to establish the effectiveness of the drug for any new uses. For new uses, the Research Team provided recommendations for the proposed indication(s) and recommended dosage regimen.

[2] Center for Medicare and Medicaid Services-designated compendia; Lexicomp Online (Walters Kluwer Lexi-Drugs); Micromedex (Truvent Analytics Micromedex Drug DEX), and the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium.

[3] Professional organizations include, but are not limited to, the American Society for Clinical Oncology (ASCO); American Society for Hematology (ASH); American Association for Cancer Research (AACR).

12.0 REFERENCES

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[4] When final, this guidance will represent the FDA's current thinking on this topic.

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Signatures

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