CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-137

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)

DATE RECEIVED: February 22, 2007	**DESIRED COMPLETION DATE:** April 1, 2007	**OSE CONSULT #:** 2007-435

TO: Robert Justice, MD
Director, Division of Drug Oncology Products
HFD-510

THROUGH: Denise Toyer, Pharm.D., Deputy Division Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Kellie Taylor, Pharm.D., M.P.H., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Fludarabine Phosphate Injection **NDA#:** 22-137	**NDA SPONSOR:** Ebewe Pharma

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence sent to the Sponsor concerning this review. If you have further questions or need clarifications, please contact Sam Chan, Project Manager, at 301-796-2283.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
(DMETS; White Oak 22, Mail Stop 4447)
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: April 30, 2007

NDA#: 22-137

NAME OF DRUG: Fludarabine Phosphate Injection, 50 mg/2 mL

NDA SPONSOR: Ebewe Pharma

I. INTRODUCTION:

This consult was written in response to a request from the Division of Drug Oncology Products (HFD-510), for assessment of the proposed label and labeling of Fludarabine Phosphate Injection. A container label, carton, and insert labeling were provided for review and comment. The Sponsor did not submit a proprietary name for the proposed Fludarabine Phosphate Injection, and therefore DMETS was not consulted to assess a proprietary name for this product.

PRODUCT INFORMATION

Fludarabine Phosphate Injection is an antineoplastic agent indicated for the treatment of adult patients with B-cell chronic lymphocytic lymphoma (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The recommended adult dose is 25 mg/ m^2 administered intravenously over a period of approximately 30 minutes daily for five consecutive days. Each five day course of treatment should commence every 28 days. Dosage reduction for patients with moderate impairment of renal function is required. According to MICROMEDEX, the Department of Pharmacy [redacted], recommends infusing Fludarabine (maximum concentration of 10 milligrams/milliliter) intravenously in 100 milliliters of standard intravenous piggyback fluids (i.e., dextrose 5% in water, normal saline).[1] Given the concentration of Fludarabine Phosphate Injection (25 mg/mL), it appears that dilution of the injectable solution prior to administration is recommended in practice. b(4)

Currently, there are two formulations of Fludarabine Phosphate approved for use in the United States: a lyophilized powder for injection (50 mg per vial) and an injectable solution (50 mg/2 mL). The only difference between the currently marked Fludarabine Phosphate Injection and the proposed product is the use of excipients in the proposed formulation of Fludarabine Phosphate Injection: [redacted] b(4)

[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

The proposed Fludarabine Phosphate Injection is supplied in individually packaged vials containing 50 mg/ 2 mL. The vials should be stored under refrigeration (36 F to 46 F). After opening, the contents should be used within 8 hours because the product contains no antimicrobial preservative.

II. RISK ASSESSMENT:

A. Database & Literature Searches

Because Fludarabine Phosphate for Injection and Fludarabine Phosphate Injection products are currently marketed, DMETS conducted a search of the medication error literature and FDA's Adverse Event Reporting System (AERS) to identify post-marketing safety reports of medication errors that could relate to the proposed labels and labeling of the product. Analysis of these reports is used to identify areas of improvement related to the label and labeling of the proposed Fludarabine Phosphate Injection product.

The MedDRA High Level Group Term (HLGT) "Medication Errors" and the tradename "Fludara" and active ingredients "Fludarabine" and "Fludarabine Phosphate" were used as search criteria. A total of 28 cases were returned. A review of the cases identified a total of 11 medication errors relating to Fludarabine use. The remaining cases described other adverse drug events, pregnancy exposures unrelated to medication error, and suicides (n=12), or medication errors related to other concomitant drug therapies (n=5).

Additionally, a search of the medication-error related literature[2] identified 1 published report of a Fludarabine medication error not captured in the AERS cases. In total 12 cases were evaluated; details are included in Appendix A. The errors related to name confusion (n=6), dosing of Fludarabine (n=2), confusion related to look-alike carton or container labels (n=2), and incorrect administration (n=1). These errors are discussed in the following section

B. Safety Evaluator Risk Assessment

In reviewing the proposed labels of this product, DMETS analyzed 12 cases of medication errors relating to the following types of confusion.

1. Name confusion (n=6)

   The errors resulting from name confusion occurred between the proprietary name, Fludara, or the established name, Fludarabine, with the following names: FUDR (Floxuridine) (n=4); Flumadine (n=1); and Navelbine (Vinorelbine Tartrate) (n=1).

   The Floxuridine and Fludarabine mix-ups are particularly concerning because the erroneous administration of either antineoplastic agent may be harmful to patients. The proprietary (**FUDR** and **Fluda**ra) and established (**Flox**uridine and **Fluda**r**abine**) names share a number of the same letters (bolded for emphasis) which creates a strong similarity between the names; a factor that was stated as contributing to the medication error in one of the reports. In three cases, the name confusion resulted in Fludarabine administration via a direct line to the hepatic line for 5 or 7 days. In one of these cases, the patient required hospitalization to undergo testing and monitoring. In the other two cases the physician did not attribute any adverse events as a

[2] ISMP's Medication Safety Alert! Acute Care, Ambulatory Care, Nursing, Consumer and Canada editions. 1996-2006.

consequence of the error, though the patients in each case died of liver failure two weeks and five days following the error. In the other two cases of Floxuridine - Fludarabine confusion, the error was caught prior to administration.

Fortunately, reports of Floxuridine and Fludarabine name confusion appear to be declining, as no reports were identified since 1999. This may be due to increased practitioner familiarity with the drugs, increased awareness of the potential for name confusion between these two products, or general changes in clinical practices surrounding antineoplastic therapy. Fludara was approved in 1991, and reports of name confusion are clustered from 1992 to 1999. Based on this trend, DMETS will continue to monitor post-marketing safety reports and assess the name similarity of FUDR/ Floxidurine and Fludarabine as a potential source of error for the proposed Fludarabine Phosphate Injection product.

The remaining two cases of name confusion (Fludarabine with Flumadine; Fludarabine with Navelbine) were both attributed to practitioner-based causes (namely knowledge deficits and busyness of the pharmacist) and would not appear to have direct implications to the label or labeling of the proposed product. Details are provided in Appendix A for completeness.

2. Dosing Errors (n=3)

All three cases of Fludarabine dosing errors resulted in the patients receiving higher dosages of the drug then intended. In one report, a 51-year old patient received doses of Fludarabine equal to 38 mg/m^2 (BSA not provided) for four days instead of a total daily dose of 38 mg. The patient was hospitalized 5 days after completion of the treatment cycle with neutropenia, weakness, nausea and vomiting, with dehydration. In another report a 23 month-old patient received two Fludarabine doses of approximately 220 mg, and experienced hepatotoxicity. The final report describes a 76-year-old patient received 100 mg/ m^2 of Fludarabine for four days instead of 25 mg/ m^2 as intended.

These cases did not describe in detail the factors contributing to this error, and at this time DMETS does not believe the errors to be attributable to the label or labeling of the currently market Fludarabine products. As such, DMETS could not use these cases to identify areas of improvement related to the label and labeling of the proposed Fludarabine Phosphate Injection product.

3. Look-alike Labels (n=2)

There were two cases describing the potential for medication errors resulting from the look-alike container and carton labels.

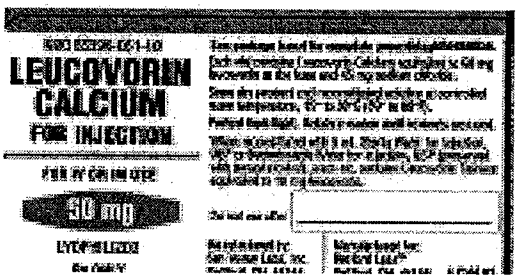
The first case was filed with the Agency in 1997, and the reporter noted that vials of Leucovorin 50 mg/vial, manufactured by Bedford Labs, look "very similar" to vials of Fludara 50 mg/vial, manufactured by Berlex. The reporter noted that the labels had "a white background with black print and a blue stripe." The case did not include an image of the labels and DMETS did not obtain the labels from 1997. However, DMETS obtained the most current version of Bedford Labs' Leucovorin and Berlex's Fludara® labels, and noted the similar appearance of the current labels is as described in the 1997 report (see Table 1 page 5). DMETS also noted that Ebewe Pharma's proposed container label for Fludarabine Phosphate Injection utilizes a [redacted] b(4) background with [redacted] (See Table 1 page 5). As such, the labels of the

proposed product were reviewed to determine if the labels look similar to the Leucovorin product.

DMETS noted that the color [redacted] the proposed Fludarabine Phosphate Injection label is a slightly different shade than that used on the Leucovorin label, and is prominently displayed on the container label of both products (see Table 1 below). However, the Leucovorin and Fludarabine labels use different layouts (horizontal blue stripe versus [redacted] and the text is displayed in different colors (black versus [redacted] Additionally, the proposed Fludarabine Phosphate Injection is a solution form product that requires refrigeration while Leucovorin is a lyophilized powder that is stored at room temperature. DMETS also notes that no actual errors have resulted from the similar appearance of Leucovorin and Fludara labels, and these products are both lyophilized powders stored at room temperature. As such, DMETS believes that the differences in layout and the differences in product characteristics adequately minimizes the potential for the similarity in color scheme to lead to product selection errors.

b(4)

Table 1: Side-by-Side Label Comparison

Bedford Labs' Leucovorin 50 mg Vial Label	Fludarabine Phosphate Injection Ebewe's Proposed Vial Label:
	[redacted] b(4)
	Fludara 50 mg Vial Label
	[redacted] b(4)

The second case also described a potential for error as a result of look-alike labels. This reporter stated that the carton labels of Vinorelbine Tartrate Injection 50 mg/5 mL and Fludarabine 50 mg (lyophilized powder), both manufactured by Sicor, look "exactly the same." The reporter noted that the cartons use the same color scheme, format, and font; the cartons are physically the same size; and that the products overlap in strength ("50 mg"). The pharmacist that reported this error felt that the similar appearance of the products could lead to mix-ups when stocking the product, and, if put away incorrectly, subsequently lead to selection errors when preparing chemotherapy orders. A faxed image (black and white) of the products was included with the report. DMETS reviewed the images of Sicor's cartons and does not believe that this potential risk applies to the proposed carton label of Fludarabine Phosphate Injection which utilizes a different layout than Sicor. Additionally, DMETS does not believe that Ebewe Pharma currently markets any products in the United States, thus eliminating the potential for confusion between Ebewe

Pharma products that have similar trade dress. However, should the Sponsor decide to market other products in the United States (particularly chemotherapeutic agents), this risk may be worth considering when developing container and carton labels.

4. Incorrect administration (n=1)

One case was identified in which a 30 year-old-patient was administered Fludarabine over 36 hours, instead of the intended IV bolus administration. No contributing factors were described in the report. DMETS has no reason to believe at this time that the label or labeling of the product contributed to this error. Consequently, DMETS could not use this case to identify areas of improvement related to the label and labeling of the proposed Fludarabine Phosphate Injection product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and labeling of Fludarabine Phosphate Injection, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS' recommendations are informed by analysis of the post-marketing safety reports of medication errors relating to the nomenclature, labels, and labeling of drug products, and more specifically, the Fludara and Fludarabine products currently marketed in the United States. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. [redacted] b(4)

2. [redacted] b(4)

B. CARTON LABELING

1. [redacted] b(4)

2. [redacted] b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Proprietary Name Review 5

Appendix A. Medication errors identified in AERS and the literature

Source ISR Date Setting Outcome	Root Cause	Narrative
1772840-9 6/21/1996 Hospital (FL) No AE attributed to error	Name Confusion	FAMILY MEMBER REPORTED A 60 YEAR OLD MALE PATIENT WHO WAS HOSPITALIZED FOR TREATMENT OF CANCER (STOMACH AND LIVER). FLUDARA WAS INADVERTENTLY GIVEN (RATHER THAT 5FU) THROUGH DIRECT LINE TO THE HEPATIC ARTERY. THE PATIENT WAS EVENTUALLY DISCHARGED TO HOME FOR FIVE DAYS, RE-ADMITTED AND DIED AFTER TWO WEEKS IN THE HOSPITAL. ACCORDING TO THE REPORTER, THE PATIENT'S CAUSE OF DEATH WAS LIVER FAILURE. THE PHYSICIAN REPORTS THAT THE PATIENT WAS BEING TREATED FOR LIVER METASTASES FROM A PRIMARY PANCREATIC CANCER. FLUDARA WAS INADVERTENTLY GIVEN RATHER THAN FUDR (FLOXURIDINE) AT A DOSE OF 20MG IA DAILY X 5 DAYS (TOTAL DOSE = 100MG ; BODY SURFACE AREA = 1.5M). ACCORDING TO THE PHYSICIAN, THERE WAS NO ADVERSE EVENT ASSOCIATED WITH THE FLUDARA ADMINISTRATION. AN AUTOPSY REVEALED EXTENSIVE CANCER INCLUDING THE LIVER, LUNGS AND LYMPH NODES. THERE WAS NO EVIDENCE OF ANY DRUG TOXICITY.
3300413-5 7/9/1999 (event date May 1995) Hospital (MD) No AE attributed to error	Name Confusion	Family member reported that a 60-year-old female patient was hospitalized for treatment of cancer (stomach and liver). Fludara (dose 20 mg, BSA 1.5 m^2) was inadvertently administered rather than 5FU through direct line to the hepatic artery and continued for 5 days. The patient was eventually discharged to home for 5 days, re-admitted and died after two weeks in the hospital. According to the reporter, the patient's cause of death was liver failure. An autopsy revealed extensive cancer including the liver, lungs, and lymph nodes, and no evidence of drug toxicity. The physician did not attribute any adverse events to the erroneous administration of Fludara.
AERS 4515920-7 5/19/1995 Hospital Patient was hospitalized for testing	Name Confusion	An order was written for FUDR 20 mg. The Pharmacist entered Fludara 20 mg into the computer. The 60 year-old female patient received the wrong medication through the hepatic artery for seven consecutive days. The reporter stated that contributing factors were: lack of familiarity with the drugs, generic names that sound fairly similar and the similarity of the consonants in the two names. The pharmacy has a policy that the chemo agents entered into the computer and the written chemo profile have to be checked by another pharmacist; this had been done. The patient's daughter, who is a Pharmacist, had been in her mother's room several times when the dug was being administered. In speaking to her mother's oncologist about Fludara, which was on the label, it became known that the patient had been receiving the wrong drug. The oncologist called the pharmacy director and it was confirmed from the chemo profile that the patient had been given Fludara instead of FUDR.
AERS 4608360-3 12/29/1992 Error discovered prior to administration	Name Confusion	The order for FUDR was misinterpreted and transcribed as Fludarabine, which is another antimetabolite. The pump was actually filled and delivered to the patient before the error was caught. Neither Pharmacy staff nor Nursing staff were able to catch this Medication Error. The error was caught by store-room pharmacist who noticed a large dose of Fludarabine was taken from stock. The store-room pharmacist questioned the Oncology Pharmacist who checked the chart and discovered the error.

AERS 4606772-5 2/1/1992 Hospital Error discovered prior to administration	Name Confusion	A resident physician called the Pharmacist to find out the name of the new flu product and was told Flumadine. Another resident called and asked a different Pharmacist the dose of Fludarabine and was told 25 mg/ m^2 per day x 5 days. This physician then ordered Fludarabine 40 mg IV QD x 5 days. When it arrived on the floor the nurse called the physician to let them know that he/she could not hang chemotherapy. At that time the physician realized he had made an error.
ISMP Medication Safety Alert! - 2/10/99 Hospital No outcome detail provided	Name Confusion	An order for Fludara (fludarabine phosphate) was received. A technician saw Navelbine (vinorelbine tartrate) in the refrigerator and asked a nearby pharmacist (who was busy doing several things) if it was the same as Fludara. The busy pharmacist replied "yes". The technician prepared the incorrect drug, Navelbine, but affixed a label for the intended drug, Fludara. The same preoccupied pharmacist checked the final product but did not notice the error and the wrong drug was dispensed an administered to a patient.
5045705-7 6/1/2006 Hospital Hepatotoxicity	Dosing Error	A 23 month old female (9.3 kg) patient received "too much" Fludarabine Phosphate due to a medication error. The report states that the patient received "most of" two doses of 220 mg per 24 hours. The patient experienced hepatotoxicity. No additional details were provided.
3750249-6 [redacted] Hospital	Dosing Error	A 76 year old female patient received, in error, Fludara 100 mg/ m^2 x 4 days instead of the prescribed Fludara dose of 25 mg/ m^2. The patient was hospitalized approximately one week after the incorrect doses were administered with transient neutropenic fever. The duration of hospitalization was reported to be 2 weeks.
3936905-5 [redacted] Hospital AEs and hospitalization	Dosing Error	51-year-old female weighing 51 kg inadvertently received an overdose of Fludara and rituximab during her first treatment cycle for Non-Hodgkin's Lymphoma. The patient received Fludara on days 1-5 at a dose of 38 mg/ m^2 instead of a total dose of 38 mg/day. She also received a rituximab dose on day #3 at a dose of 565mg/ m^2 instead of 375 mg/ m^2. Five days after the treatment cycle, the patient was hospitalized with WBC count of 0.5 (baseline WBC 3.4), severe weakness, nausea and vomiting, with dehydration.
4168176-1 08/26/1997 Hospital -	Look-alike labels	The vials of Leucovorin 50mg/vial (Bedford Labs) and Fludara 50mg/vial (Berlex) look very similar, which could lead to the wrong drug being given. Both labels have a white background with black print and a blue stripe.
5263580-2 03/12/1997 Hospital, teaching –	Look-alike Labels	A chemotherapy pharmacist was pulling Fludarabine 50 mg injection when she noticed that the Vinorelbine 50 mg injection looked exactly the same [redacted] The report notes that the labels have the same color scheme, same format, same font, same sized box, and the same strength. Even though she did not pull the Vinorelebine in error, the pharmacist felt that the risk of confusion is "very high." Additionally, when the pharmacy technician was processing a delivery from the Wholesaler the similarity was noticed. Compounding the issue, the Vinorelbine and Fludarabine cartons were packed together in the same bubble wrap from the Wholesaler. When the package was opened, both chemo products were about to be put into one bin. The report states that if the products had been put away incorrectly, the pharmacist could have e pulled the wrong chemotherapy drug since the boxes look "exactly the same.

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AERS 4420574-4 Hospital Hospitalization on day 11 with high fever, chills, and positive blood culture for corynebacterium.	Incorrect administration	A 30-year-old female patient was prescribed fludarabine 25 mg/ m^2 IV (days 1-5) and cytarabine 2 gm/ m^2 IV (days 1,3,4, and 5) for AML. Fludara was intended to be given as IV bolus, however the drug was inadvertently administered as a continuous infusion for the first 36 hours. Once the error was identified, the patient was witch to 25 mg/ m^2 IV beginning on day 3, 4, and 5.

b(6)

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/s/

Kellie Taylor
5/4/2007 02:29:25 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/4/2007 03:16:25 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/4/2007 03:43:11 PM
DRUG SAFETY OFFICE REVIEWER