

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-273

SUMMARY REVIEW

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Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, M.D.
Subject	Cross Discipline Team Leader/Division Director Summary Review
NDA/BLA # Supplement #	22273
Applicant Name	Xanthus Pharmaceuticals now Antisoma Pharmaceuticals
Date of Submission	11/19/07
PDUFA Goal Date	9/19/08 extended due to late submission of QTc study
Proprietary Name / Established (USAN) Name	Fludara/fludarabine
Dosage Forms / Strength	Film coated tablet
Proposed Indication(s)	Fludarabine 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 or after treatment with at least one standard alkylating-agent containing regimen.
Action/Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Dr. Martin Cohen
Statistical Review	Dr. Chia-Wen Ko
Pharmacology Toxicology Review	Dr. Lee-Ham
CMC Review/OBP Review	Dr. Josephine Jee
Microbiology Review	N/A
Clinical Pharmacology Review	Dr. Gene Williams
DDMAC	JuWon Lee
DSI	Dr. L. Ball's memo
CDTL Review	This review is both the DD and CDTL memo.
OSE/DMETS/DRISK	Nancy Carothers/Jodi Duckhorn
OSE/DDRE	
OSE/DSRCS	
Other	

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

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DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

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Signatory Authority Review Template

1. Introduction

On November 15, 2007, Xanthus Pharmaceuticals, Inc., now Antisoma Pharmaceuticals submitted this 505 b2 NDA for a new oral formulation of fludarabine for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen.

2. Background

On November 15, 2007, Xanthus Pharmaceuticals, Inc., now Antisoma Pharmaceuticals submitted this 505 b2 NDA for a new oral formulation of fludarabine for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen.

On April 18, 1991, Bayer Healthcare received approval for the intravenous injection formulation of fludarabine based on results from two small single-arm phase 2 studies (one single center and one multi-center) enrolling patients who were refractory to at least one prior standard alkylating-agent containing regimen. In both studies patients were treated for 5 days every 28 days with doses ranging from 15-40 mg/m².

From the intravenous injection formulation label:

The overall objective response rates were 48% and 32% in the MDAH and SWOG studies, respectively. The complete response rate in both studies was 13%; the partial response rate was 35% in the MDAH study and 19% in the SWOG study. These response rates were obtained using standardized response criteria developed by the National Cancer Institute CLL Working Group and were achieved in heavily pre-treated patients. The ability of FLUDARA FOR INJECTION to induce a significant rate of response in refractory patients suggests minimal cross-resistance with commonly used anti-CLL agents.

The median time to response in the MDAH and SWOG studies was 7 weeks (range of 1 to 68 weeks) and 21 weeks (range of 1 to 53 weeks) respectively. The median duration of disease control was 91 weeks (MDAH) and 65 weeks (SWOG). The median survival of all refractory CLL patients treated with FLUDARA FOR INJECTION was 43 weeks and 52 weeks in the MDAH and SWOG studies, respectively.

Rai stage improved to Stage II or better in 7 of 12 MDAH responders (58%) and in 5 of 7 SWOG responders (71%) who were Stage III or IV at baseline. In the combined studies, mean hemoglobin

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concentration improved from 9.0 g/dL at baseline to 11.8 g/dL at the time of response in a subgroup of anemic patients. Similarly, average platelet count improved from 63,500/mm³ to 103,300/mm³ at the time of response in a subgroup of patients who were thrombocytopenic at baseline.

Intravenous fludarabine is used as a single agent or in combination with other agents to treat adult patients with CLL. Multiple randomized studies have suggested fludarabine's effectiveness as a single agent and in combination therapy, particularly with rituximab and cyclophosphamide. The National Comprehensive Cancer Network Guideline (2/08) lists fludarabine as a single agent or in combination as an effective treatment for first or second line CLL disease.

3. CMC/Device

The Chemistry, Manufacturing, and Control Review for this NDA states that this application is approvable. For details see review by Dr. Josephine Jee. There are no outstanding issues and no recommended phase 4 commitments.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology information was submitted with this application. There are no outstanding issues. The pharmacology/toxicology review team did review the labeling prior to approval.

5. Clinical Pharmacology/Biopharmaceutics

From the clinical pharmacology review:

“The oral dose was selected to approximate the AUC of the IV product and results in an AUC of approximately 95% of that of the IV product.”

“Consistent with the package insert for the IV product, the focus of the pharmacokinetics program was to characterize 2F-ara-A pharmacokinetics. Absolute bioavailability of 2F-ara-A from the oral formulation is approximately 60%. T_{max} is approximately 1.6 hours and terminal half-life is the same across routes of administration: approximately 22 hours.”

“Food did not effect bioavailability (AUC and C_{max}).”

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The sponsor submitted the results from 1 phase 2 single-arm study (ME96029) with supporting data from 2 additional studies.

From Dr. Cohen's review:

One phase 2 study was performed in patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. Study ME96029 enrolled 78 patients who received oral fludarabine at a dose of 40 mg/m² daily for 5 days every 28 days. The overall objective response, according to NCI criteria, was 51%, including 18% complete responses (CR) and 33% partial responses (PR). The overall response rate, according to IWCLL criteria, was 46%, including 21% CRs, best case analysis (all patients who responded to treatment were deemed a responder, regardless of when they discontinued treatment) and 41% NCI criteria (18% CR) and 35% IWCLL criteria (19% CR), worst case analysis (patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR. Duration of response and time to progression were not assessed in study ME96029. However, the mean number of treatment cycles for patients in study ME96029 was 5.1, with a mean daily dose of fludarabine of 38 mg/m²/day which was slightly below the target dose of 40 mg/m²/day. Since cycles were repeated at a minimum of every 28 days and since remissions often occurred after 1 cycle of treatment a minimum estimated remission duration is >16 weeks.

Two other studies, conducted in previously-untreated B-CLL patients, support the activity of oral fludarabine with respect to time dependent efficacy endpoints. Study 303080 included 81 patients treated with fludarabine 40 mg/m² PO daily for five days every four weeks. The remission rate was 80%, NCI criteria (12% CR) and 72% IWCLL criteria (37% CR), best case analysis and 69% NCI criteria and 61% IWCLL criteria, worst case analysis. Median duration of remission was 22.6 months and median time to treatment progression was 29.2 months.

Study LRF CLL4 (sponsor analysis after initial data submission) included 124 assessable non-randomized patients who received fludarabine 40 mg/m² PO daily for five days every four weeks and 57 non-randomized patients who received IV fludarabine. The overall response rate (CR + nPR + PR) was 90% for IV fludarabine and 71% for oral fludarabine. Median response duration was 779 days for oral fludarabine and 701 days for IV fludarabine. It is emphasized that these are non-randomized comparisons. Patients receiving oral fludarabine were enrolled when that drug became available and were older, with poorer performance status, more advanced disease, and lower platelet and hemoglobin levels.

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These results were compared with efficacy data from three studies of IV fludarabine, 20+ mg/m² daily for five days every 28 days in previously treated CLL patients and two studies of IV fludarabine in previously-untreated B-CLL patients, CALGB 9011, (175 patients) and CLL 101 study (53 patients).

Efficacy data from two of the former studies, the subset of 48 refractory B-CLL patients from MDAH (T83-1275) and 32 refractory or relapsed B-CLL patients from SWOG [83-78] were the basis of approval of the IV fludarabine formulation. The third study (CLL 101 study) included 53 previously-treated B-CLL patients who received fludarabine 25 mg/m² IV daily for five days every four weeks. b(4)

The overall response rates in the pivotal study of oral fludarabine in relapsed or refractory patients with B-CLL (ME96029) were slightly better than the rates observed following treatment with IV fludarabine in the MDAH (T83-1275) study (48%, 13% CRs using NCI criteria, best case analysis and 23% (8% CR) using NCI criteria, worst case analysis) and in refractory or relapsed patients with B-CLL from the SWOG (83-78) study (32% using NCI criteria 13% CR), best case analysis and 19% using NCI criteria (13% CR), worst case analysis). When response was assessed using IWCLL response criteria and compared with results from the subset of previously-treated patients with B-CLL in Study CLL 101 Study) using IWCLL criteria, the overall response rate in the pivotal study of oral fludarabine (ME96029) was lower than that observed with IV fludarabine (35% in ME96029), versus 45% in CLL 101 Study. b(4)

The median duration of response in relapsed or refractory patients with B-CLL treated with IV fludarabine ranged from > 37 weeks (SWOG, 83-78) to > 41 weeks (MDAH, T83-1275), and median survival time ranged from 45 weeks (MDAH, T83-1275) to 54 weeks (SWOG, 83-78).

For studies in previously-untreated patients, the criteria used to assess response varied among the studies. The overall response rate seen in the study of oral fludarabine (303080) was as good as or better than the overall response rates seen in the studies of IV fludarabine, which ranged from 61% (CALGB criteria) to 70% (IWCLL criteria).

The median duration of response for previously-untreated patients ranged from 19 months following IV fludarabine (CALGB 9011) to 22.6 months following oral fludarabine (303080). Median time to progression ranged from 17.4 months following IV fludarabine (CALGB 9011) to 29.2 months following oral fludarabine (303080).

The results from the 3 submitted studies demonstrated that the oral fludarabine formulation can produce complete and partial responses. The major study did not include information on the durability of these responses. However, the other two studies did have information as Dr. Cohen states on "time dependent efficacy endpoints." Study 303080 included information on median duration of remission which was 22.6 months and Study LRF CLL4 had information on median response duration which was 779 days for oral fludarabine.

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In neither study was the effect on the time-dependent efficacy endpoint short (less than 60 days). Time-to-event endpoints are difficult to interpret in single arm trials because they reflect the natural history of the disease as well as the effect if any of the drug. Dr. Cohen reviewed the results from several studies for the intravenous formulation. The results suggest that the effect seen on the time-to-event endpoints were similar for the oral formulation compared with the intravenous formulation.

Dr. Chia-Wen Ko, the statistical reviewer wrote,

"In this reviewer's opinion, the efficacy results from the pivotal study ME96029 have not provided a substantial evidence from a statistical point of view to support oral Fludara for the proposed indication. Although the observed overall response rate of 51% based on the National Cancer Institute Criteria for B-CLL may seem to be comparable to the ones seen with the IV Fludara (48% in the study by M. D. Anderson Cancer Center, and 32% in the study by Southwestern Oncology Group), cross-study comparisons may not be adequate considering the differences in dose, treatment duration, and use of supportive therapy between the studies. In addition, there was no follow-up of patients after completion of study and information about duration of response or survival could not be obtained.

Furthermore, data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression collected in the single-arm study B820 are difficult to quantify in the absence of a control group, and any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the Fludara treated patients did not receive IV or oral Fludara according to randomization."

Dr. Ko does not recommend approval based on the trial data. She correctly points out the flaws in the data. However, her review does not consider the wealth of published data with the intravenous formulation of fludarabine that exists.

I concur with Dr. Cohen that this oral fludarabine formulation should receive accelerated approval. Due to the fact that the dosing is different for the oral formulation compared with the intravenous, I recommend that we include a statement in the labeling that the dosing is different for the different formulations.

8. Safety

From Dr. Cohen's review:

AE's associated with fludarabine treatment have been well described. The safety database of oral fludarabine phosphate provides data on 502 patients including 474 patients treated with oral fludarabine phosphate tablets. In addition to the 78 patients in the pivotal trial (Study ME96029) and 81 patients in Study 303080. 92 B-CLL, NHL and low grade NHL patients were treated with oral fludarabine phosphate monotherapy in pharmacokinetic studies. Additionally, limited safety data are available from Study LRF CLL4, where 122 B-CLL patients received oral fludarabine phosphate monotherapy. Finally, post-marketing safety surveillance data are available from over _____ patients treated with oral fludarabine phosphate in regions of the world where this formulation is approved.

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Across all of these studies oral fludarabine phosphate therapy was generally well tolerated. The most commonly reported adverse events reported across all studies included myelosuppression, fever, cough, nausea, vomiting, diarrhea, asthenia, anorexia, and infections. These events were usually mild or moderate in severity with non-hematological Grade 3-4 events occurring in up to 8% of patients and hematological grade 3-4 toxicities occurring in up to 25% of patients. Adverse events and toxicities observed with oral fludarabine did not significantly differ from the adverse event profile of the IV formulation, with the exception of mild/moderate nausea, vomiting and diarrhea which seemed to occur at slightly higher rates in patients treated with oral formulation. Post-marketing experience in clinical practice with oral fludarabine over the past 6 years shows that, based on voluntary reported adverse drug reactions during the marketed period, the safety profile of oral fludarabine has not significantly changed from when oral fludarabine was initially approved in 2000 in the UK.

I concur with Dr. Cohen's comments regarding the safety of oral fludarabine.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee meeting.

The intravenous formulation of fludarabine is known for many years to be one of the most effective agents in the treatment of CLL. This submission is for an oral formulation which demonstrated a consistent effect in more than one study. In addition, the safety of oral fludarabine is similar to the safety of the intravenous formulation.

10. Pediatrics

Oral fludarabine has Orphan Drug status and therefore a waiver or deferral is not necessary.

11. Other Relevant Regulatory Issues

A new Division of Scientific Investigation audit was deemed not necessary because for major trial the data had been reviewed by staff in 2001 and the other two studies were supportive and from the literature. Please see Dr. Ball's memo for details.

From Dr. Cohen's review:

The clinical studies included in NDA 22-273 for oral fludarabine were sponsored by Schering AG (now known as Bayer Schering Pharma). The sponsor (Xanthus) has requested certification of financial interests for the clinical investigators who participated in the oral fludarabine clinical trials from Bayer Schering Pharma. To date Xanthus has not been provided this certification. They

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have no reason to believe, however, that the clinical investigators were the recipient of significant payments or compensation, as defined in 21 CFR Part 54, that would have affected the outcome of the clinical study. Xanthus confirms that they have no financial relationship with any study investigators; have made no payments directly to any of these individuals and no listed investigator owns Xanthus stock.

In addition, the major study for approval was conducted from 10/1/96 to 5/11/98 and nearly completed at the time of publication of the final rule on financial disclosure. Per the Guidance for Industry Financial Disclosure, studies completed prior to February 2, 1999 have a reduced need to gather financial information.

Therefore the applicant has provided sufficient financial disclosure.

12. Labeling

All relevant disciplines provided input on the labeling and negotiated successfully with the sponsor.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

I recommend accelerated approval with commitment from the sponsor to conduct a randomized trial to provide evidence of clinical benefit.

The sponsor has agreed to conduct a multicenter, randomized active control study of oral fludarabine phosphate monotherapy versus chlorambucil monotherapy in patients with previously untreated progressive CLL. The primary endpoint of the study will be progression-free survival. The sponsor anticipates submitting a protocol in the first quarter of 2009 and enrolling patients starting in the third quarter of 2009. The sponsor anticipates enrollment will complete in 2012 and that completion of the study will occur in 2013. The Sponsor anticipates submitting the final study report, SAS datasets and labeling in 2014.

- Risk Benefit Assessment

Fludarabine is an effective drug that has been used for many years using an intravenous formulation. The side effect profile is well known. Approval of this application provides a convenient oral formulation which decreases the time that patients will have to spend in the clinic.

- Recommendation for Postmarketing Risk Management Activities
Continued surveillance for adverse events
- Recommendation for other Postmarketing Study Commitments

As above

- Recommended Comments to Applicant

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Ann Farrell
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