**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 103946/5083

**SUPPLEMENT APPROVAL**

October 16, 2009

sanofi-aventis U.S. LLC
Attention: Brenda W. Kozan
Assistant Director
Regulatory Research and Development Portfolio
sanofi-aventis U.S. Inc.
9 Great Valley Parkway
PO Box 3026
Malvern, PA 19355

Dear Ms. Kozan:

Your request to supplement your biologics license application for Elitek (rasburicase) to include a new indication in adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid has been approved.

This submission also fulfills your postmarketing commitments (PMCs) numbers 4, 5, 6, and 9, identified in the July 12, 2002, approval letter under STN BL 103946/0. The commitments addressed are as follows:

**PMC #4**

- To develop a quantitative ELISA for antibodies in patient sera for use in clinical safety studies and to submit information demonstrating assay sensitivity (with limit of quantification defined in mass units), specificity, reproducibility, robustness, and ruggedness. Until the final assay is validated, serum samples will be collected and banked for future analysis. The protocol for assay methods and the validation plan for the new ELISA will be submitted to CBER by August 31, 2002. The complete validation data will be available by March 31, 2003, and a final report submitted to CBER by September 30, 2003.

**PMC #5**

- To submit information on the enzyme inhibition (antibody neutralization) assay to be used in clinical safety studies, demonstrating assay sensitivity, specificity, reproducibility, robustness, and ruggedness. This information will include assessments of optimal concentrations of reagents to detect antibodies, and assurance that pharmacological levels of product in serum samples do not influence detection of antibodies. The protocol for assay methods and the validation plan for the new antibody

neutralization assay will be submitted to CBER by December 30, 2002. The validation data will be available by June 30, 2003, and a final report submitted to CBER by September 30, 2003.

**PMC #6**

- To design an appropriate antigen-specific assay for IgE assessment, such as RAST or radioallergosorbent testing, and to use the specific assay for IgE, in addition to the ELISA and enzyme inhibition assays, at appropriate times during the clinical trials. Until the specific test for IgE is appropriately designed and validated, serum samples will be collected and banked for future analysis. The protocol for assay methods and the validation plan for the antigen-specific IgE assay will be submitted to CBER by December 30, 2002. The complete validation data will be available December 30, 2003, and a final report submitted to CBER by March 31, 2004.

**PMC #9**

- To conduct a study designed to assess the comparative safety and efficacy of the approved dose and schedule of rasburicase with a regimen of sequential rasburicase and allopurinol. This study will be conducted in adults and will enroll a sufficient number of subjects to randomize at least 60 patients (approximately 30 per treatment arm), following a short induction course of rasburicase (two days treatment). The objectives of this trial will include comparison of the adequacy of control of plasma uric acid concentration and comparison of the toxicity profile for the two regimens, including the comparability of the immunogenicity profile of rasburicase in the two regimens. This study will use the all-patient schedule to assess immunogenicity. Plasma uric acid levels will be assessed at pre-specified time points in all patients and should be sufficient to assess maintenance of uric acid over various time points throughout rasburicase treatment. Maintenance of uric acid levels will be as defined in the package insert. The protocol will include a detailed description of the analyses to characterize the following in each arm and a comparison between arms:

  a. The incidence, duration, and type of immune responses (i.e., IgG, IgE, neutralizing);

  b. Clinical toxicity associated with an immune response;

  c. Maintenance of uric acid levels at 4, 24, 48, 72 and 96 hours after first dose of rasburicase;

  d. Impact of immune response on maintenance of uric acid levels, i.e. pharmacodynamic impact. The protocol will include a detailed description of all analyses intended to assess these objectives.

  A draft protocol will be submitted by August 31, 2002, and the final protocol will be submitted by November 30, 2002. Accrual to the study will be completed by September 30, 2004. The final study report will include an assessment of the binding (IgG),

neutralizing antibody, and IgE immunogenicity profile, the impact of immunogenicity on safety and efficacy, and the analysis of the comparable safety and efficacy of the sequential regimen to the approved regimen. The final study report will be completed and submitted by June 30, 2005.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since Elitek (rasburicase) was approved on July 12, 2002, we have become aware of spontaneous postmarketing adverse event reports of cardiac arrhythmias, four of which resulted in death, associated with Elitek (rasburicase). We consider this information to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the unexpected serious risk of cardiac toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to do the following:

1. Reanalyze the dataset for clinical trial TDU4730 "Safety, tolerance pharmacokinetic and pharmacodynamic study of single ascending doses of SR29142 (rasburicase) in healthy subjects" to include categorical analyses that summarize the number of subjects with QTc intervals > 450 ms, > 480 ms, and > 500 ms and change from baseline in QTc > 30 ms and > 60 ms. The analyses will include the mean change from pre-dose baseline (with two-sided 90% CI) on ECG parameters including QTc at each time point following drug administration.

The Final Report will include the following items:

a. Copies of the report(s) for any other clinical trials of the effect of product administration on the QT interval that have been performed.

b. Electronic or hard copy of the amended report.

c. Electronic or hard copy of the clinical protocol.

d. Electronic or hard copy of the Investigator's Brochure.

e. Annotated Case Report Forms (CRFs).

f. A Define file which describes the contents of the electronic datasets.

g. Electronic datasets as SAS transport files in CDISC SDTM format and all the SAS codes for the analyses.

h. Narrative summaries and CRFs for any:
   i. Deaths
   ii. Serious adverse events
   iii. Episodes of ventricular tachycardia or fibrillation
   iv. Episodes of syncope
   v. Episodes of seizure
   vi. Adverse events resulting in the subject discontinuing from the clinical trial

i. A completed Highlights of Clinical Pharmacology Table.

The timetable you submitted on October 7, 2009, states that you will conduct this review of clinical trial data according to the following milestone:

**Final Report Submission:** by April 16, 2010

Submit the final report to your BLA 103946. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you

include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## CONTENT OF LABELING

The final printed labeling must be identical to the enclosed labeling. Marketing the product with final printed labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We note your October 14, 2009 submission included final content of labeling [CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the enclosed labeling text. Within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

If you have any questions, contact the Senior Regulatory Health Project Manager, Erik Laughner, M.S., at (301) 796-1393.

Sincerely,

/Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Package Insert Labeling