May 25, 2010

Submission Request c/o Mary Anne Bergman
National Comprehensive Cancer Network
275 Commerce Dr, Suite 300
Fort Washington, PA 19034

RE: Request for Addition of Prophylactic Rasburicase Use in High or Potential Risk TLS Patients in NHL

Name: Julia Petses
Company/Organization: sanofi-aventis US
Address: 55 Corporate Dr. Bridgewater, NJ 08807
Phone: (908) 981-7287
Email: julia.petses@sanofi-aventis.com
Date of request: May 25, 2010
NCCN Guidelines Panel: NHL

Dear Ms. Bergman:

As the National Comprehensive Cancer Network (NCCN) Non-Hodgkin's Lymphomas (NHL) Panel reviews the NCCN Clinical Practice Guidelines in Oncology for NHL, we respectfully request consideration of the inclusion of Elitek (rasburicase) for tumor lysis prophylaxis in patients at high or potential risk of developing tumor lysis syndrome (TLS).

Request for Addition of Prophylactic Rasburicase Use in High or Potential Risk TLS Patients

This request is for the NHL Panel to consider for review the addition of Elitek (rasburicase) to the NCCN Clinical Practice Guidelines as TLS prophylaxis in patients with NHL at high or potential risk for TLS. Elitek is indicated for the initial management of plasma uric acid levels in pediatric and 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.[1] Guidelines for the management of TLS, published in 2008 by Coiffier et al., recommend hydration plus initial management with rasburicase in patients at high risk of developing TLS.[2] These guidelines define NHL patients at high TLS risk as those having Burkitt (and Burkitt-like) lymphoma, lymphoblastic lymphoma, and B-acute lymphoblastic leukemia (ALL). Further, patients with intermediate grade NHL (e.g., diffuse large B cell lymphoma) are considered at intermediate (potential) risk for TLS, and so are patients with chronic lymphocytic leukemia (CLL) with white blood cell count (WBC) between 10,000-100,000/mm^3 who are treated with fludarabine or biologic agents (e.g., rituximab). In the pivotal trial in adult patients for which Elitek received approval for use in adults, eligible patients with "very aggressive" and "aggressive" lymphoma were considered at high and potential risk for TLS, respectively.[3] (Aggressiveness of the disease was based on the REAL classification of lymphoid malignancies.[4]) In this trial, plasma uric acid response rate with rasburicase (0.2 mg/kg/day for 5 days) was significantly higher than with allopurinol (300 mg/day for 5 days) in adult patients with hematologic malignancies who were at high risk (89% vs. 68%; P=0.0012) for TLS or were hyperuricemic (90% vs. 53%; P=0.0151) at baseline. Additionally, two studies in pediatric patients with leukemia or lymphoma (including

children and adolescents with NHL) with fully developed TLS or at high risk forTLS/hyperuricemia of malignancy found Elitek to be safe and effective[5], as well as a safe and effective alternative to allopurinol[6].

Specific change recommended

In the tumor lysis syndrome section of the NHL practice guidelines, expand the use of rasburicase for tumor lysis prophylaxis in patients at high or potential risk of developing TLS to settings other than salvage therapy post-allopurinol failure or presence of renal impairment (i.e., removal of the qualifying statement 'rising uric acid despite allopurinol, high creatinine').

FDA Status

Elitek is indicated for the initial management of plasma uric acid levels in pediatric and 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. [1]

Rationale for recommended change

NHL patients with Burkitt lymphoma, lymphoblastic lymphoma, and B-ALL are considered at high risk of developing TLS as per current guidelines, while patients with intermediate grade NHL (e.g., diffuse large B cell lymphoma) are considered at intermediate (potential) risk for TLS, and so are patients with CLL with WBC between 10,000-100,000/mm^3 who are treated with fludarabine or biologic agents (e.g., rituximab)[2], whereas in the Elitek pivotal adult indication trial, Elitek was found to be superior to allopurinol in controlling plasma uric acid in adult patients with hematologic malignancies who were at high risk for TLS (including patients with very aggressive and aggressive lymphoma per REAL classification) or were hyperuricemic at baseline. [3]

Literature support

1. Elitek [package insert]. Bridgewater, NJ: sanofi-aventis U.S.; 2009.
2. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767-2778.
3. Cortes J, Seiter K, Maziarz RT, et al. Superiority of rasburicase versus allopurinol on plasma UA control in adult patients with hematologic malignancies at risk of developing tumor lysis syndrome: results of a randomized comparative phase III study [poster]. Presented at: American Society of Hematology Annual Meeting, December 6-9, 2008, San Francisco, CA.
4. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*. 1994;84(5):1361-1392.
5. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*. 2001;97(10):2998-3003.
6. Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. *J Clin Oncol*. 2001;19:697-704.