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FDA Approves Elitek(R) (rasburicase) for Management of Plasma Uric Acid Levels in Adults with Leukemia, Lymphoma, and Solid Tumors Receiving Anti-Cancer Therapy

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BRIDGEWATER, N.J., Oct. 16 /PRNewswire-FirstCall/ -- Sanofi-aventis U.S. announced that the U.S. Food and Drug Administration (FDA) has granted marketing approval for Elitek® (rasburicase) to be used for the initial management of plasma uric acid (PUA) levels in adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis syndrome (TLS) and subsequent elevations of plasma uric acid.

Today's FDA approval was based on pivotal Phase 3 trial results which demonstrated that Elitek significantly reduced PUA levels when compared to the current standard of care (oral allopurinol) in adults with hematologic cancers at risk for the potentially life-threatening complication of TLS. Patients considered at high risk for TLS either had an elevated level of PUA (hyperuricemia) due to a malignancy, or were diagnosed with a very aggressive hematologic malignancy (leukemia or lymphoma).

"The approval of Elitek in adult patients with cancer now provides physicians with an important new option for managing elevated plasma uric acid which could result in tumor lysis syndrome, a potentially life-threatening complication that can develop from anti-cancer therapy," said principal investigator Dr. Jorge Cortes, Professor of Medicine and Deputy Chair, Department of Leukemia at The University of Texas, M.D. Anderson Cancer Center, in Houston, Texas.

Clinical TLS was defined by changes in at least two or more laboratory parameters, namely hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, along with at least one of the following clinical events occurring within 7 days of treatment: renal failure/injury, need for dialysis, and/or serum creatinine increase greater than 1.5 x ULN, arrhythmia or seizure (according to the Cairo-Bishop criteria).

"We are very proud that Elitek - which has already been shown to bring significant treatment benefits to pediatric patients at risk of developing this complication - has now been approved by the U.S. Food and Drug Administration to help adult patients as well," said Dr. Paul Chew, Senior Vice President, U.S. Chief Science Officer/Chief Medical Officer of sanofi-aventis U.S. "This approval is also an example of sanofi-aventis's commitment to further exploring our existing compounds and the potential benefit they bring to patients with serious diseases, such as in the areas of oncology and hematology."

Study Background

The primary objective of the multi-center, open-label, randomized, parallel group comparative study was to compare the safety and the effectiveness of three treatments (intravenous Elitek (rasburicase) alone daily for 5 days, intravenous Elitek daily for day 1 to day 3 followed by oral allopurinol daily for day 3 to day 5, and oral allopurinol alone daily for 5 days) in achieving uric acid response rate. The daily dose of Elitek was 0.20 mg/kg, while that of allopurinol was 300 mg. The PUA response rate was defined as the proportion of patients with PUA levels less than or equal to 7.5 mg/dL from day 3 to day 7 after initiation of treatment.

Results showed that among patients treated with Elitek alone or followed by oral allopurinol, uric acid levels were less than or equal to 2.0 mg/dL in 96% of patients (at 4 hours of the day 1 dose). There were no patients in either Elitek group with documented failure to control uric acid. In patients treated with Elitek alone (n=92), the PUA response rate was 87%, which was higher than that seen with patients treated with oral allopurinol alone (n=91) at 66% (p=0.0009), a statistically significant difference, or those treated with the Elitek/oral allopurinol combination (n=92) at 78%. The Elitek versus Elitek/oral allopurinol combination difference in PUA response rate was not statistically significant.

Antihyperuricemic treatment was extended beyond five days in 4.4% of patients treated with oral allopurinol alone and 6.5% of patients treated with the Elitek/oral allopurinol combination, versus 0% of patients receiving Elitek alone. Clinical TLS occurred in 3% of Elitek-treated patients, 3% of Elitek/oral allopurinol-treated patients, and 4% of oral allopurinol-treated patients.

Hypersensitivity reactions occurred in 4.3% of patients treated with Elitek alone and 1.1% of patients treated with the Elitek/oral allopurinol combination. Hypersensitivity reactions included arthralgia, injection site irritation, peripheral edema, and rash. The most common Grade 3/4 related adverse reactions regardless of relationship to study drug were sepsis (5.4% / 6.5% / 4.4%), hypophosphatemia (4.3% / 6.5% / 6.6%), anxiety (3.3% / 0% / 0%), abdominal pain (3.3% / 4.3% / 2.2%), hyperbilirubinemia (3.3% / 2.2% / 4.4%) and increased alanine aminotransferase (3.3% / 4.3% / 2.2%) in the Elitek, Elitek/oral allopurinol and oral allopurinol arms, respectively. Of note, all patients were receiving anti-cancer chemotherapy and/or biologic anti-cancer agents for their primary disease. The following serious adverse reactions occurred with a difference in incidence of greater than or equal to 2% in patients receiving Elitek compared to patients receiving oral allopurinol: pulmonary hemorrhage, respiratory failure, supraventricular arrhythmias, ischemic coronary artery disorders, and abdominal and gastrointestinal infections.

Based on the results of the above study, Elitek is now indicated at a daily dose of 0.20 mg/kg intravenously for up to 5 days for the initial management of plasma uric acid levels in adults with leukemia, lymphoma and solid tumors receiving anti-cancer therapy expected to result in tumor lysis syndrome and subsequent elevation of plasma uric acid.

About Elitek®

A recombinant urate oxidase enzyme, Elitek is the first recombinant uricolytic agent approved in the U.S. to maintain PUA levels in patients receiving anti-cancer therapy. Elitek rapidly catabolizes circulating uric acid into allantoin, a highly soluble by-product that is easily excreted by the kidneys. Elitek reduces circulating uric acid levels as soon as 4 hours after the first dose. Elitek was initially approved by the U.S. FDA in 2002 to manage PUA levels in pediatric patients receiving anti-cancer treatment and at risk for TLS. Visit www.elitekinfo.com for more information about Elitek. Elitek® is also commercially available under the brand name of Fasturtec® outside the United States.

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 syndrome and subsequent elevation of plasma uric acid. Elitek is indicated for only a single course of treatment.

IMPORTANT SAFETY INFORMATION

Anaphylaxis: ELITEK can cause severe hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue ELITEK in patients who experience a serious hypersensitivity reaction.

Hemolysis: Do not administer ELITEK to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue ELITEK in patients developing hemolysis. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting ELITEK.

Methemoglobinemia: ELITEK can result in methemoglobinemia in some patients. Immediately and permanently discontinue ELITEK in patients developing methemoglobinemia.

Interference with Uric Acid Measurements: ELITEK enzymatically degrades uric acid in blood samples left at room temperature. Collect blood samples in pre-chilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection.

Among the 347 (265 pediatric; 82 adult) patients for whom all adverse reactions regardless of severity were assessed in Studies 1, 2 and 3, as well as an uncontrolled safety trial, the most frequently observed adverse reactions (incidence greater than or equal to 10%) were vomiting (50%), fever (46%), nausea (27%), headache (26%), abdominal pain (20%), constipation (20%), diarrhea (20%), mucositis (15%), and rash (13%).

Among the 275 adult patients in Study 4, hypersensitivity reactions occurred in 4.3% of patients treated with ELITEK alone and 1.1% of patients treated with the ELITEK/oral allopurinol combination. Hypersensitivity reactions included arthralgia, injection site irritation, peripheral edema, and rash. The most common Grade 3 or 4 adverse reactions regardless of relationship to study drug in the 3 arms of Study 4 (ELITEK alone; ELITEK combined with oral allopurinol; oral allopurinol alone) were sepsis (5.4%; 6.5%; 4.4%), hypophosphatemia (4.3%; 6.5%; 6.6%), anxiety (3.3%; 0%; 0%), abdominal pain (3.3%; 4.3%; 2.2%), hyperbilirubinemia (3.3%; 2.2%; 4.4%), and increased alanine aminotransferase (3.3%; 4.3%; 2.2%), respectively.

The following serious adverse reactions occurred with a difference in incidence of greater than or equal to 2% in patients receiving ELITEK compared to patients receiving oral allopurinol in randomized studies (Study 1 and Study 4): pulmonary hemorrhage, respiratory failure, supraventricular arrhythmias, ischemic coronary artery disorders, and abdominal and gastrointestinal infections.

For full prescribing information, including boxed WARNING, please visit <http://products.sanofi-aventis.us/elitek/elitek.html>.

About Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a metabolic complication that can result either spontaneously or following treatment of certain types of rapidly-growing cancers, particularly leukemia or lymphoma. The syndrome develops when a particularly large volume of tumor cells are rapidly destroyed by treatment, releasing their contents - including nucleic acids, which are then eventually catabolized into uric acid - into the bloodstream. Elevated levels of plasma uric acid (hyperuricemia) is a serious condition that can lead to kidney impairment if not controlled. Prevalence of TLS varies among patients with different types of cancer, but occurs more often with malignancies that are particularly sensitive to anti-cancer therapy.

About sanofi-aventis

Sanofi-aventis U.S. is an affiliate of sanofi-aventis, a leading global pharmaceutical company that discovers,

develops and distributes therapeutic solutions to help improve the lives of patients. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY). For more information, visit: www.sanofi-aventis.us or www.sanofi-aventis.com.

Forward Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include financial projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future events, operations, products and services, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans" and similar expressions. Although sanofi-aventis' management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of sanofi-aventis, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in sanofi-aventis' annual report on Form 20-F for the year ended December 31, 2008. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.

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