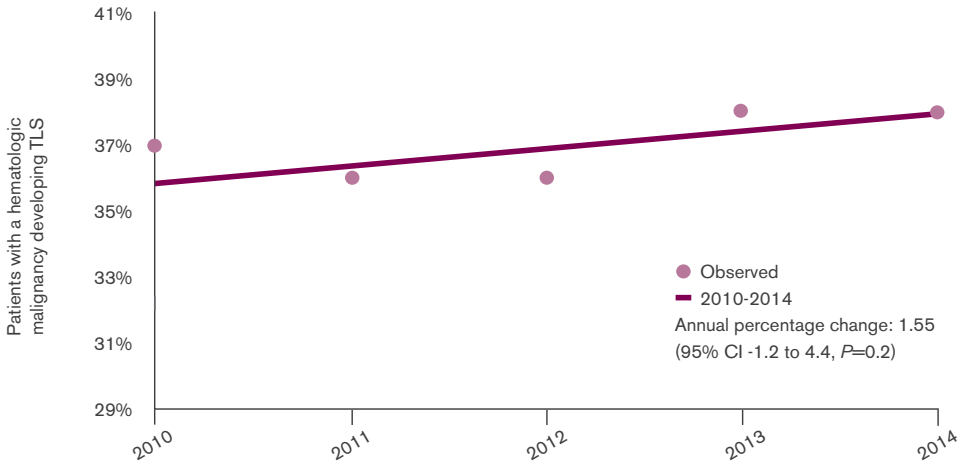
PROTECT YOUR PATIENTS AT HIGH RISK FOR TLS AND HYPERURICEMIA

Dear Healthcare Provider,

Tumor lysis syndrome (TLS)–related hyperuricemia is an oncologic emergency that can be avoided with proactive management. Between 2010-2014, 37.1% of patients with hematologic malignancies developed TLS. This is based on data from the National Inpatient Sample Database, the largest publicly available all-payer inpatient database in the United States.[1]

Incidence of TLS in patients with hematologic malignancies[1]



37%
incidence of TLS per year from 2010-2014*

Adapted from Pathak et al.

*A total of 15,051 cases of TLS were identified among the 40,494 patients with hematologic malignancies during the study period.

Importantly, not all patients who are at risk for TLS have elevated uric acid levels before starting anticancer therapy.[2] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend to best manage TLS and hyperuricemia, anticipate it and initiate treatment prior to anticancer therapy.[3]

Choose rasburicase: Recommended for patients at intermediate and high risk for development of TLS associated with hyperuricemia.[4]

ELITEK is the only recombinant urate-oxidase approved by the FDA for the initial management of uric acid in patients with leukemia and lymphoma who are receiving anticancer therapy.[5]

Important Safety Information

WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

- **Hypersensitivity Reactions: ELITEK can cause serious and fatal 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.**

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information, including boxed WARNING.

ELITEK® rasburicase IV Infusion

ELITEK given prophylactically was proven to prevent rising uric acid levels in patients at high and intermediate risk of TLS and hyperuricemia[5,6]

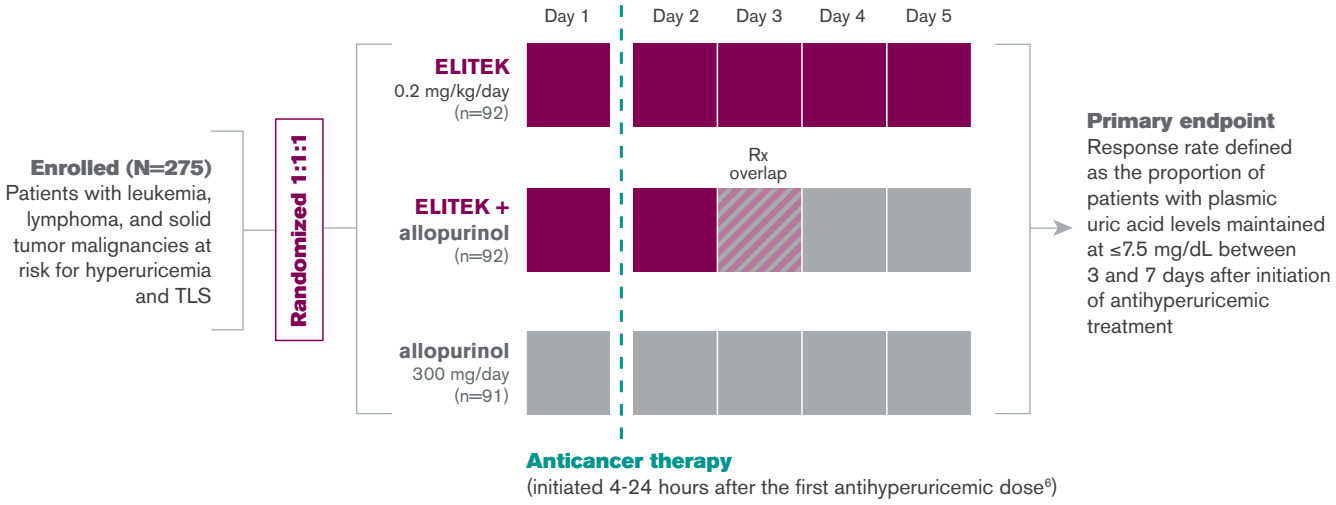
- **9 out of 10** patients were at high risk
- **82%** of patients had normal uric acid levels (≤7.5 mg/dL)

Patients meeting at least 1 of the following criteria were enrolled in a pivotal trial[6-8]:

High risk	Intermediate risk
Aggressive lymphoma/leukemia (defined by REAL) • DLBCL • Anaplastic large cell lymphoma • Peripheral T-cell lymphomas • Burkitt lymphoma • Lymphoblastic lymphoma • CLL	Aggressive lymphoma/leukemia, not limited to the REAL definition, with LDH ≥2x the upper limit of normal
AML	Any stage III to IV lymphoma or leukemia
CML in blast crisis	Stage I or II disease with bulky lymph node/tumor (>5 cm) involvement
High-grade MDS with >10% bone marrow blast involvement	
Elevated plasma uric acid levels at baseline (>7.5 mg/dL)	

Prophylactic use of ELITEK was studied in a robust phase 3 trial, where ELITEK was initiated prior to anticancer therapy[5,6]

Pivotal trial design[5,6]



AML=acute myeloid leukemia; CLL= chronic lymphocytic leukemia; CML= chronic myeloid leukemia; DLBCL=diffuse large-B-cell lymphoma; LDH=lactate dehydrogenase; MDS=myelodysplastic syndrome; REAL= Revised European American Classification of Lymphoid Neoplasms.

Important Safety Information (cont'd)

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

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information, including boxed WARNING.

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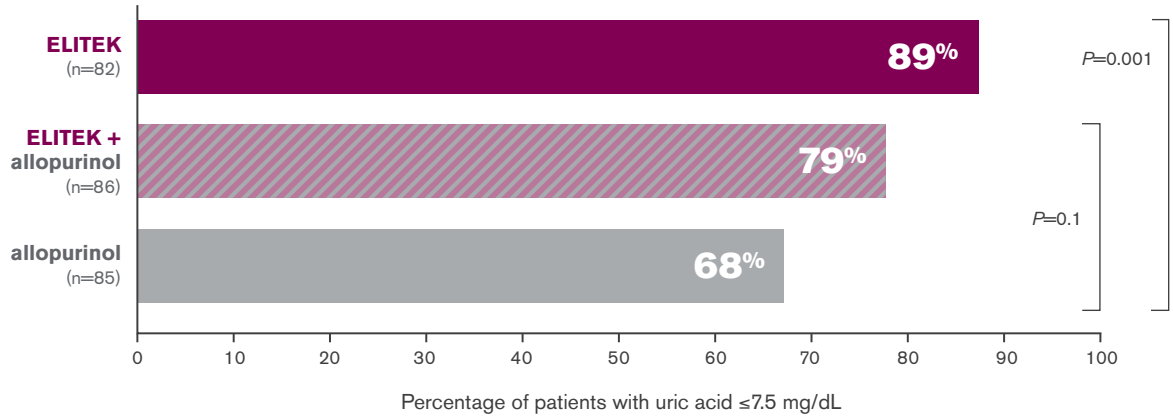
ELITEK given prophylactically maintained normal uric acid levels in significantly more high-risk patients vs allopurinol[6]

High-risk patients maintaining normal uric acid (≤7.5 mg/dL) between 3-7 days after initiation of antihyperuricemic treatment[6,9]



These results were consistent with the overall patient population (primary endpoint): 87% (n=92) of patients receiving ELITEK maintained uric acid ≤7.5 mg/dL vs 66% (n=91) of patients receiving allopurinol (*P*=0.001). ELITEK + allopurinol maintained normal uric acid in 78% (n=92) of patients (*P*=NS) vs allopurinol.[6]

Unlike allopurinol, ELITEK maintained normal uric acid levels in 100% of assessable patients[5]

Documented failure rates in hyperuricemic and nonhyperuricemic patients

- The ELITEK, ELITEK + allopurinol, and allopurinol arms had 13%, 15%, and 19% missing uric acid samples, respectively. The uric acid failure status in those patients is unknown
- No patients taking ELITEK required hyperuricemic treatment beyond 5 days, vs 6.5% of patients taking ELITEK + allopurinol and 4.4% taking allopurinol alone

NCCN CLL/SLL Guidelines: Consider prophylaxis with rasburicase in patients receiving venetoclax with high tumor burden and elevated baseline uric acid[3]

Important Safety Information (cont'd)

- **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.**

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ELITEK has a proven safety profile[5]

Adverse reactions ≥10% in any ELITEK arm and ≥5% allopurinol

	ELITEK (n=92)		ELITEK + allopurinol (n=92)		allopurinol (n=91)	
Adverse Reaction*	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Nausea	57.6	1.1	60.9	1.1	54.9	2.2
Peripheral edema	50	2.2	43.5	3.3	42.9	6.6
Vomiting	38	1.1	37	0	30.8	1.1
Anxiety	23.9	3.3	17.4	0	17.6	0
Abdominal pain	21.7	3.3	33.7	4.3	25.3	2.2
Hypophosphatemia	17.4	4.3	22.8	6.5	16.5	6.6
Hyperbilirubinemia	16.3	3.3	14.1	2.2	7.7	4.4
Pharyngolaryngeal pain	14.1	1.1	20.7	0	9.9	0
Sepsis	12	5.4	7.6	6.5	4.4	4.4
Fluid overload	12	0	6.5	0	3.3	1.1
Increased ALT	10.9	3.3	27.2	4.3	17.6	2.2
Hyperphosphatemia	9.8	0	15.2	0	8.8	1.1

*Events were reported and graded according to the NCI-CTC Version 3.0 and presented as preferred terms MedDRA version 10.1.

Indication

ELITEK is indicated for the initial management of uric acid in patients with leukemia and lymphoma who are receiving anticancer therapy, only for a single course of treatment.

Important Safety Information (cont'd)

- Among the 347 (265 pediatric; 82 adult) patients for whom all adverse reactions (ARs) regardless of severity were assessed in Studies 1, 2 and 3, as well as an uncontrolled safety trial, the most common ARs (≥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 plus oral allopurinol. Hypersensitivity reactions included arthralgia, injection site irritation, peripheral edema, and rash. The most common Grade 3-4 ARs regardless of relationship to study drug in Study 4 (ELITEK alone; ELITEK plus 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 ARs occurred with a difference in incidence of ≥2% in patients receiving ELITEK vs. oral allopurinol in Study 1 and Study 4: pulmonary hemorrhage, respiratory failure, supraventricular arrhythmias, ischemic coronary artery disorders, and abdominal and gastrointestinal infections.

Please see accompanying full Prescribing Information, including boxed WARNING.

References: 1. Pathak R, Giri S, Aryal M. Recent trends in the incidence and outcomes of tumor lysis syndrome in hematological malignancies: data from 2010-2014 National Inpatient Sample. *Blood.* 2017;130:3390. **2.** Edeani A, Shirali A. Chapter 4: Tumor Lysis Syndrome. *Onco-Nephrology Curriculum.* American Society of Nephrology. 2016. https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter4.pdf. Accessed October 19, 2018. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphomas. V.2.2019. ©National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed October 19, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** Howard SC, Jones DP, Ching-Hon P. The tumor lysis syndrome. *N Engl J Med.* 2011;364(19):1844-1854. **5.** Elitek [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2017. **6.** Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone—results of a multicenter phase III study. *J Clin Oncol.* 2010;28(27):4207-4213. **7.** Jakić-Razumović J, Aurer I. The World Health Organization classification of lymphomas. *Croat Med J.* 2002;43(5):527-534. **8.** Nicolaides C, Dimou S, Pavlidis N. Prognostic factors in aggressive non-Hodgkin's lymphomas. *Oncologist.* 1998;3(3):189-197. **9.** Data on file. Bridgewater, NJ: sanofi-aventis U.S. LLC.

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