IN PATIENTS AT HIGH RISK FOR TUMOR LYSIS SYNDROME (TLS) ASSOCIATED WITH HYPERURICEMIA

THE POWER TO PREVENT RISING URIC ACID LEVELS *IS IN YOUR HANDS*

In a phase 3 trial, ELITEK given prophylactically (prior to anticancer therapy) maintained normal uric acid levels (≤7.5 mg/dL) in significantly more high-risk patients (89%, n=82) vs allopurinol (68%, n=85) between 3 and 7 days after initiation of antihyperuricemic treatment (*P*=0.001).[1,2]

- Results were consistent with the overall study population **(primary endpoint)**: 87% (n=92) of patients receiving ELITEK vs 66% (n=91) of patients receiving allopurinol (*P*=0.001)

Indication

ELITEK is indicated for the initial management of plasma uric acid levels in patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. ELITEK is indicated only for a single course of treatment.

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

TLS IS AN ONCOLOGIC EMERGENCY WITH POTENTIALLY DEVASTATING CONSEQUENCES

TLS is caused by massive release of intracellular contents into peripheral blood that results in metabolic derangements[2]

Hyperuricemia	Hyperkalemia	Hyperphosphatemia	Hypocalcemia

Prevalent in hematologic malignancies with[2]:

- High proliferative rate
- Large cellular burden
- High sensitivity to chemotherapy or cytolytic antibody therapy

Occurs spontaneously or in response to chemotherapy or biotherapy[2]

- Usually 12 to 72 hours after the start of therapy[3]

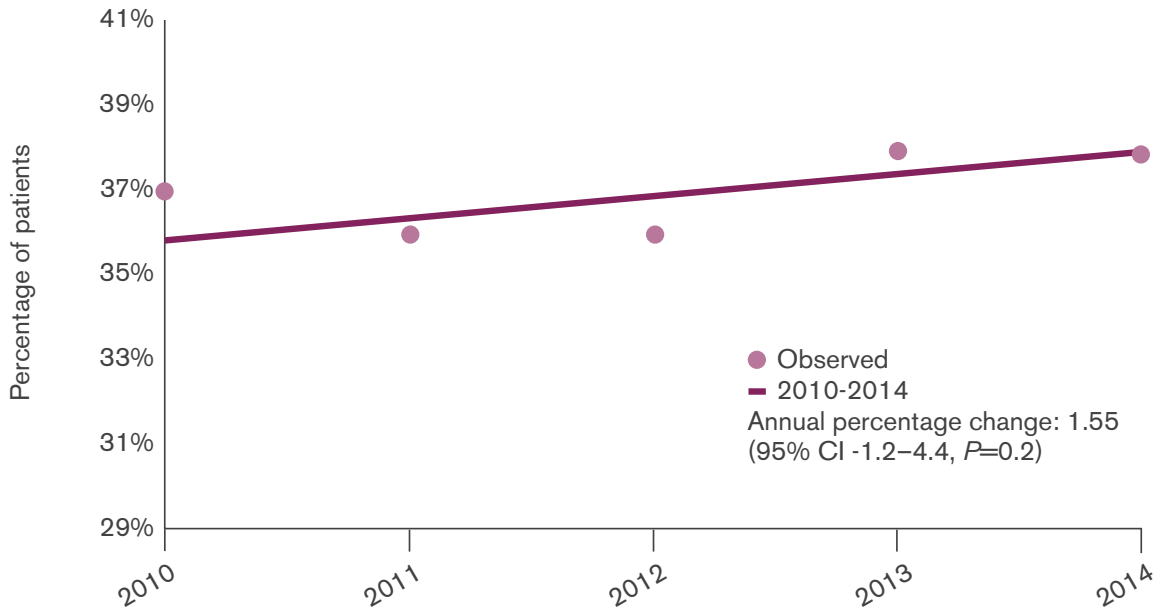
TLS associated with hyperuricemia may lead to serious clinical complications including acute renal failure, cardiac arrhythmias, loss of muscle control, seizures, or death[3]

TLS IS THE MOST COMMON DISEASE-RELATED EMERGENCY IN HEMATOLOGIC CANCERS[4]

37% of patients with hematologic malignancies developed TLS per year between 2010 and 2014[5]

- This is based on data from the National Inpatient Sample Database, the largest publicly available all-payer inpatient database
- A total of 15,051 cases of TLS were identified among the 40,494 patients with hematologic malignancies during this period

Incidence of TLS in patients with hematologic malignancies[5]



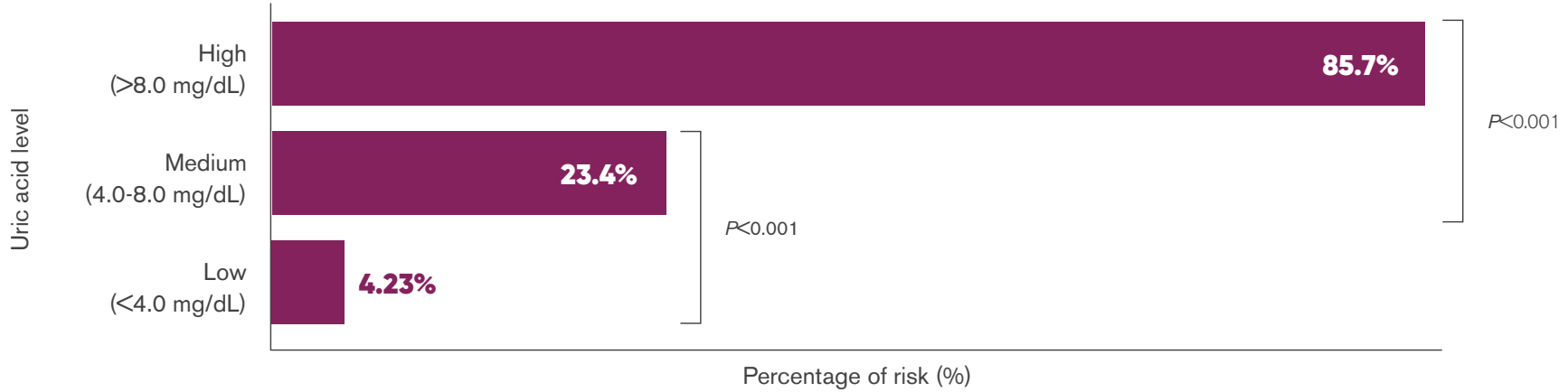
37%

incidence of TLS per year from 2010-2014

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[6]

PATIENTS WITH NORMAL URIC ACID LEVELS MAY BE AT SIGNIFICANT RISK[7]

Relationship between uric acid level and development of TLS in patients with hematologic malignancies[7]



Retrospective analysis conducted to determine the relationship between uric acid levels and TLS in 1198 patients with a hematological malignancy who were admitted for inpatient chemotherapy

Not all patients who are at risk for TLS have elevated uric acid levels before starting anticancer therapy[8]

Factors that put patients at increased risk of developing hyperuricemia and TLS include[3,6,9]:

- Bulky disease
- Lymph node involvement
- Bone marrow involvement
- Elevated LDH
- Elevated creatinine levels
- Elevated WBC count
- Renal involvement or insufficiency

Certain anticancer agents have been associated with elevated uric acid or TLS[10-24]*

Venetoclax	Ibrutinib	Lenalidomide	Bendamustine HCl	Imatinib	Obinutuzumab	Thalidomide
Vincristine sulfate†	Dasatinib	Omacetaxine	Bortezomib	Pomalidomide	Doxorubicin HCl†	Nilotinib
Rituximab†	Brentuximab vedotin	Ixazomib	Cetuximab	Carfilzomib	Romidepsin	

*This is not a comprehensive list of agents.
†Components of the R-CHOP regimen.

ELITEK WAS STUDIED IN PATIENTS AT HIGH AND INTERMEDIATE (POTENTIAL) RISK[2]

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 one of the following criteria were enrolled in the pivotal trial[2]:

High Risk[2,25,26]	Intermediate (Potential) Risk[2]
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
Elevated plasma uric acid levels at baseline (>7.5 mg/dL)	Stage I or II disease with bulky lymph node/tumor (>5 cm) involvement
High-grade MDS with >10% bone marrow blast involvement	
CML in blast crisis	

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.**

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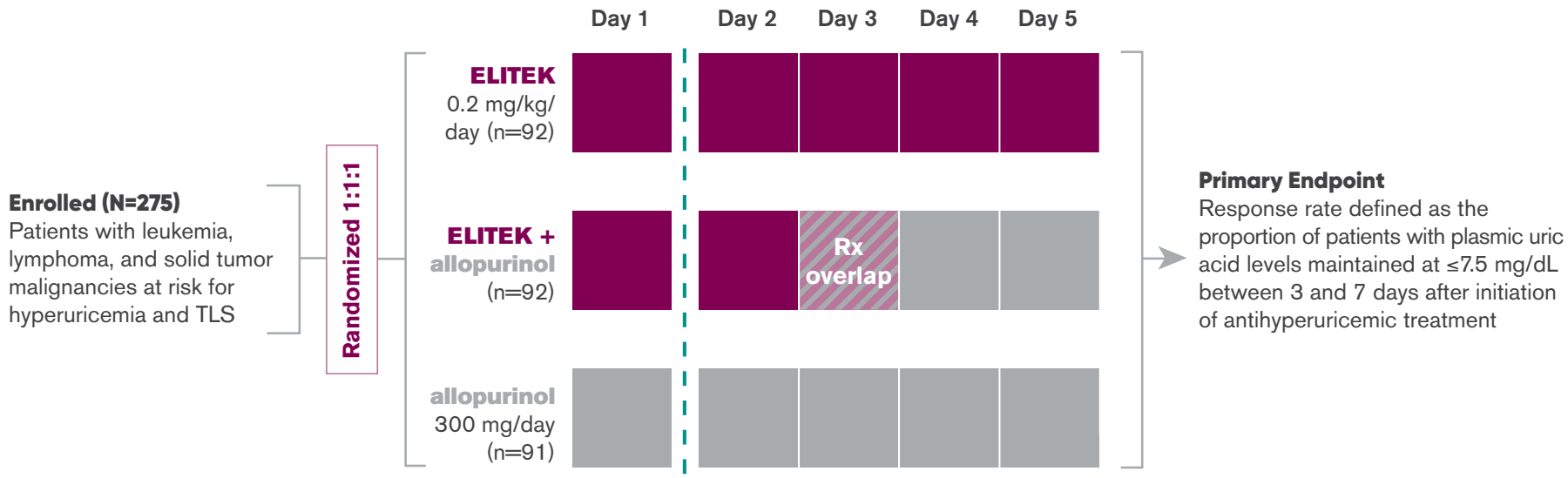
PROPHYLACTIC USE OF ELITEK WAS PROVEN IN A PIVOTAL TRIAL TO PREVENT RISING URIC ACID[2]

Antihyperuricemic therapy in all 3 arms was initiated prior to anticancer therapy[2]

- Phase 3, randomized, multicenter, open-label study

Pivotal trial design[1,2]



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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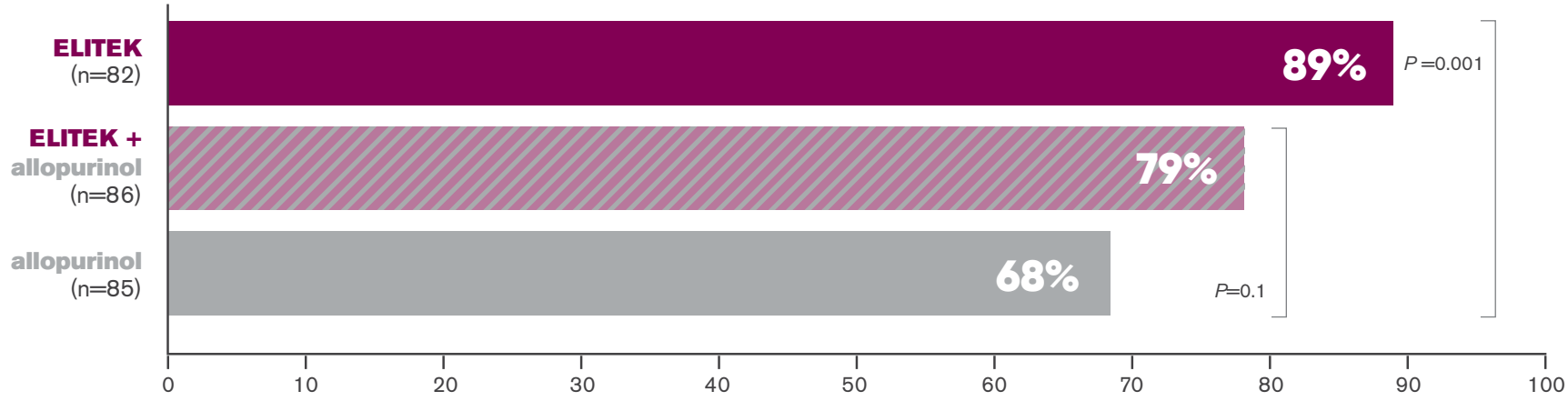
ELITEK® rasburicase IV Infusion

ELITEK GIVEN PROPHYLACTICALLY MAINTAINED NORMAL URIC ACID LEVELS IN SIGNIFICANTLY MORE HIGH-RISK PATIENTS VS ALLOPURINOL[2]

High-risk patients (%) who maintained normal uric acid levels (≤7.5 mg/dL)[2,27]



Percentage of patients with uric acid levels ≤7.5 mg/dL from Day 3 to Day 7 after initiating antihyperuricemic treatment

- Results were consistent with the overall patient population **(primary endpoint)**: 87% (n=92) of patients receiving ELITEK prophylactically maintained uric acid levels ≤7.5 mg/dL vs 66% (n=91) of patients receiving allopurinol (*P*=0.001)[2]
  - ELITEK + allopurinol maintained normal uric acid in 78% (n=92) of patients (*P*=NS vs allopurinol)[2]

ELITEK is recommended for patients at high and intermediate (potential) risk for development of TLS associated with hyperuricemia[4]

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%).

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ELITEK® rasburicase IV Infusion

UNLIKE ALLOPURINOL, ELITEK MAINTAINED NORMAL URIC ACID LEVELS IN 100% OF ASSESSABLE PATIENTS[1]

Documented failure rate in hyperuricemic and nonhyperuricemic patients[1]

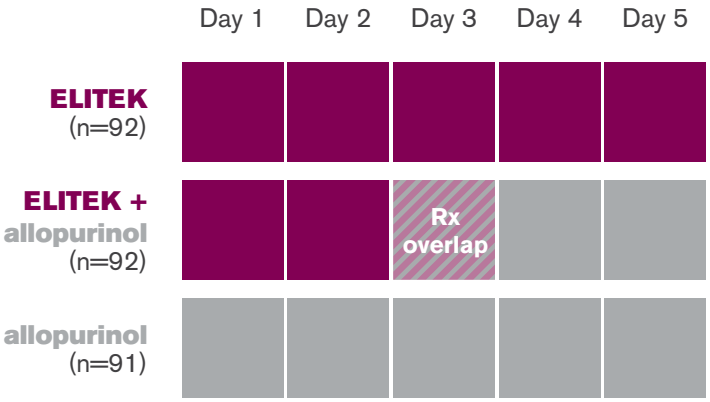
0%
ELITEK
(n=92)

0%
ELITEK + allopurinol
(n=92)

11%
allopurinol
(n=91)

- 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[1]

No patients receiving ELITEK alone required hyperuricemic treatment past 5 days[1]



Percentage of patients extended beyond 5 days of treatment

0%

6.5%

4.4%

Important Safety Information (cont'd)

- 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.

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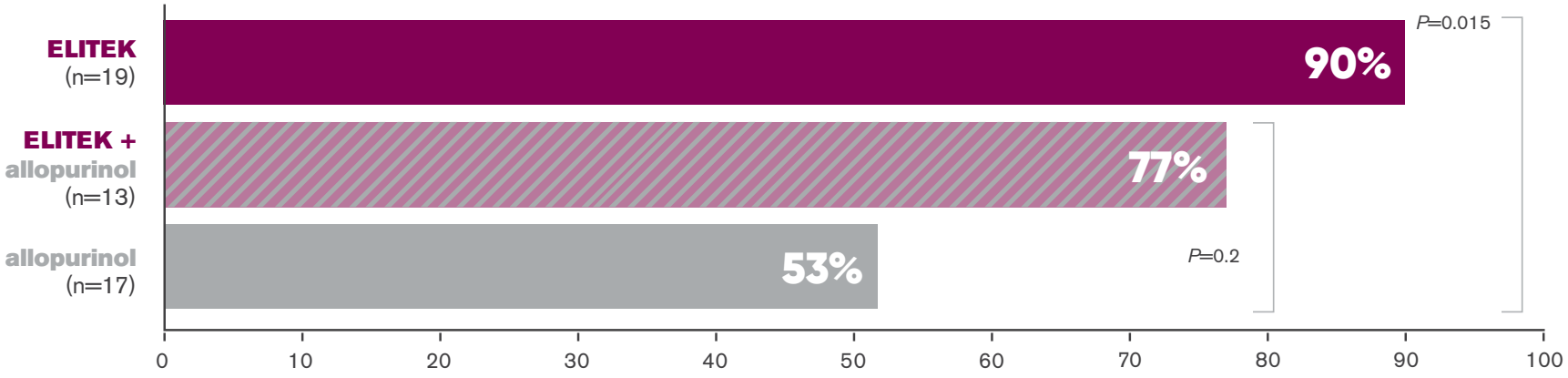
ELITEK® rasburicase IV Infusion

ELITEK GIVEN PROPHYLACTICALLY MAINTAINED NORMAL URIC ACID LEVELS IN SIGNIFICANTLY MORE PATIENTS WITH BASELINE HYPERURICEMIA VS ALLOPURINOL[2]

18% of patients were hyperuricemic (>7.5 mg/dL) at baseline and therefore considered at high risk of developing TLS[2]

96% of ELITEK patients achieved uric acid levels ≤2 mg/dL within 4 hours after their first dose vs 0% with allopurinol[1,2]

Hyperuricemic patients (%) who maintained normal uric acid levels (≤7.5 mg/dL)[2,27]



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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for CLL/SLL: Consider prophylaxis with rasburicase in patients receiving venetoclax with high tumor burden and elevated baseline uric acid[6]

SLL=small lymphocytic lymphoma.

Important Safety Information (cont'd)

- 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.

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ELITEK® rasburicase IV Infusion

ELITEK: ONCE DAILY FOR UP TO 5 DAYS[1]

Recommended ELITEK dosing: 0.2 mg/kg once daily[1]

30-minute intravenous infusion

For up to 5 days

No dose-modification requirement

- Not indicated for dosing beyond 5 days or administration of more than one course
- Do not administer as an intravenous bolus

ELITEK is available in 2 vial sizes: 1.5 mg and 7.5 mg[1]

ELITEK 1.5 mg

NDC# 0024-5150-10

3 single-dose vials each containing 1.5 mg of ELITEK and 3 ampules each containing 1 mL diluent

ELITEK 7.5 mg

NDC# 0024-5151-75

1 single-dose vial containing 7.5 mg of ELITEK and 1 ampule containing 5 mL diluent

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%).

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PROVEN SAFETY PROFILE

Per-patient incidence of selected adverse reactions[1]

	ELITEK % (n=92)		ELITEK + allopurinol % (n=92)		allopurinol % (n=91)	
Adverse Reaction*	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 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 NCI-CTC Version 3.0 and presented as preferred terms MedDRA version 10.1.

Overall incidence of adverse reactions ≥10% in any ELITEK arm and the difference between any ELITEK arm vs allopurinol ≥5%[1]

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ELITEK® rasburicase IV Infusion

ELITEK®
rasburicase
IV Infusion

PROTECT PATIENTS AT HIGH RISK
FROM RISING URIC ACID LEVELS

ELITEK: The only recombinant urate-oxidase FDA-approved for the initial management of uric acid in patients with leukemia and lymphoma who are receiving anticancer therapy[1]

Recommended: For patients at high and intermediate (potential) risk for development of TLS associated with hyperuricemia[4]

More Protective: In a phase 3 trial, ELITEK given prophylactically (prior to anticancer therapy) maintained normal uric acid levels (≤7.5 mg/dL) in significantly more high-risk patients (89%, n=82) vs allopurinol (68%, n=85) between 3 and 7 days after initiation of antihyperuricemic treatment (P=0.001).[1,2] Results were consistent with the overall study population **(primary endpoint)**: 87% (n=92) of patients receiving ELITEK vs 66% (n=91) of patients receiving allopurinol (P=0.001)

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References: 1. ELITEK [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2017. **2.** 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. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas. V.1.2019. ©National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed December 4, 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, Pui C-H. The tumor lysis syndrome. *N Engl J Med.* 2011;364(19):1844-1854. **5.** 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. **6.** 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. **7.** Cairo MS. Prevention and treatment of hyperuricemia in hematological malignancies. *Clin Lymphoma.* 2002;3(S1): S26-S31. **8.** 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. **9.** Wilson FP, Berns JS. Onco-nephrology: tumor lysis syndrome. *Clin J Am Soc Nephrol.* 2012;7(10):1730-1739. **10.** Sprycel [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015. **11.** Bose P, Qubaiah O. A review of tumour lysis syndrome with targeted therapies and the role of rasburicase. *J Clin Pharm Ther.* 2011;36(3):299-326. **12.** Belay Y, Yirdaw K, Enawgaw B. Tumor lysis syndrome in patients with hematological malignancies. *J Oncol.* 2017. https://doi.org/10.1155/2017/9684909. **13.** Treanda [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2015. **14.** Pomalyst [prescribing information]. Summit, NJ: Celgene Corporation; 2016. **15.** Adriamycin [prescribing information]. Bedford, OH: Bedford Laboratories; 2006. **16.** Ninlaro [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2016. **17.** Marqibo [prescribing information]. South San Francisco, CA: Talon Therapeutics; 2012. **18.** Venclexta [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; 2018. **19.** Adcetris [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; 2016. **20.** Synribo [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2015. **21.** Gazyva [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2016. **22.** Kyprolis [prescribing information]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc.; 2017. **23.** Istodax [prescribing information]. Summit, NJ: Celgene Corporation; 2016. **24.** Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018. **25**. Jakić-Razumović J, Aurer I. The World Health Organization classification of lymphomas. *Croat Med J.* 2002;43(5):527-534. **26.** Nicolaides C, Dimou S, Pavlidis N. Prognostic factors in aggressive non-Hodgkin's lymphomas. *Oncologist.* 1998;3(3):189-197. **27.** Data on file. Bridgewater, NJ: sanofi-aventis U.S. LLC.

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