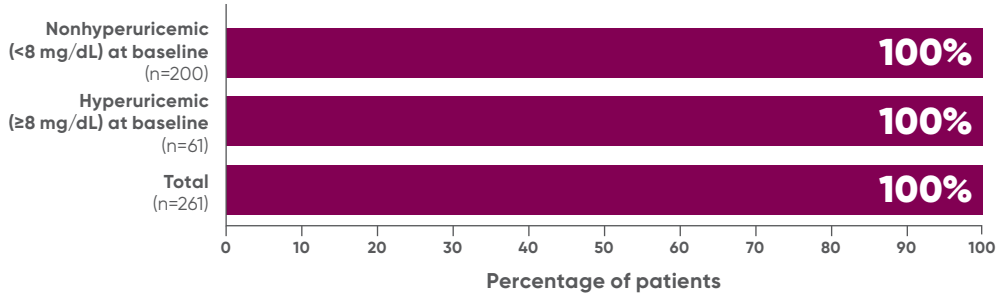
PROPHYLACTIC USE OF ELITEK WAS STUDIED IN 3 CLINICAL TRIALS TO PREVENT RISING URIC ACID IN PEDIATRIC PATIENTS[1]

- Data from studies 1, 2, and 3 were pooled and 265 patients with hematologic malignancies (acute leukemia or non-Hodgkin's lymphoma) receiving ELITEK were analyzed according to plasma uric acid levels over time[1]
- 93% (246/265) of patients (pooled) enrolled in these clinical trials were pediatric[1]
- 98% (261/265) of enrolled patients were evaluable: 77% (200/261) of patients had normal uric acid levels (<8 mg/dL) and 23% (61/261) of patients were hyperuricemic (≥8 mg/dL) at baseline[1]
- ELITEK was administered prior to and concurrent with anticancer therapy[1]
- 95% (251/265) of patients (pooled) were administered a 30-minute infusion once daily; the others (14/265) received infusions twice daily. The recommended dose of ELITEK is 0.2 mg/kg as a 30-minute IV infusion daily for up to 5 days. Dosing beyond 5 days of administration of more than one course is not recommended[1]

In 3 clinical trials, ELITEK maintained normal uric acid levels in 100% of evaluable patients by day 4[1]

Evaluable patients maintaining normal uric acid levels (≤6.5 mg/dL for patients <13 years of age or ≤7.5 mg/dL for patients ≥13 years of age) 4 days post initiation of ELITEK[1]



Maintenance was defined as uric acid levels ≤6.5 mg/dL (patients <13 years of age) or ≤7.5 mg/dL (patients ≥13 years of age) without the need for allopurinol or other agents.[1]

- Of the 261 evaluable patients in studies 1, 2, and 3 (pooled)[1]:
  - Normal uric acid levels were maintained for 92% (240/261) of patients by 4 hours, 93% (245/261) by 24 hours, 97% (254/261) by 48 hours, and 99% (260/261) by 72 hours
  - For patients with hyperuricemia (≥8 mg/dL) at baseline, uric acid levels were maintained by 72% (44/61) after 4 hours, 80% (49/61) after 24 hours, 92% (56/61) after 48 hours, and 98% (60/61) after 72 hours

Indication

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. 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.**

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

ELITEK® rasburicase IV Infusion

STUDY 1

PROPHYLACTIC USE OF ELITEK (rasburicase) WAS STUDIED IN PEDIATRIC PATIENTS AT HIGH RISK OF TLS ASSOCIATED WITH HYPERURICEMIA[2]

100%
of pediatric patients were at high risk at baseline[2]

63%
of pediatric patients had normal uric acid levels (<8 mg/dL) at baseline[2]

Patients meeting at least 1 of the following criteria were enrolled in the trial[2]:

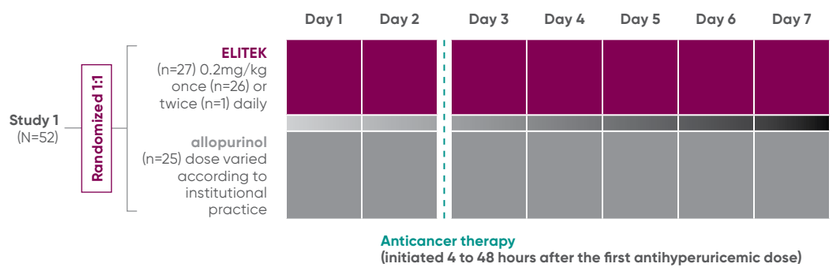
- Murphy stage III or IV NHL
- ALL with a peripheral WBC count of ≥25,000/µL at presentation
- Any childhood lymphoma or leukemia with a uric acid level of ≥8 mg/dL at the time of study entry

Additional eligibility criteria were life expectancy of ≥4 weeks and an ECOG ≤3, or a Karnofsky scale of ≥30%.[2]

Antihyperuricemic therapy in both arms was initiated prior to anticancer therapy[1]

- **Phase 3:** a randomized, multicenter, open-label, controlled study in pediatric patients (N=52) with leukemia or lymphoma at high risk for TLS associated with hyperuricemia[1,2]
- **Primary endpoint:** reduction in uric acid levels measured from the last value prior to the first dose of study drug until 4 days (96 hours) after that first dose ($AUC_{0-96\ hr}$) of ELITEK vs allopurinol[1]

Pediatric clinical trial design[1]*



*Actual deviations from study protocol occurred in 2/52 patients (anticancer therapy given to first administration of ELITEK); presumed deviations from study protocol occurred in 1/52 patients (anticancer therapy was same as first administration of ELITEK or may have been prior to ELITEK administration).[2]

ALL=acute lymphocytic leukemia; WBC=white blood cell; ECOG=Eastern Cooperative Oncology Group; NHL=non-Hodgkin lymphoma; TLS=tumor lysis syndrome; AUC=area under the curve.

Important Safety Information cont'd

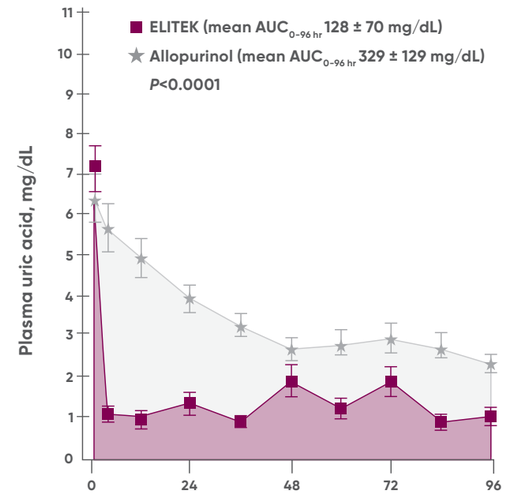
- **Hemolysis: Do not administer ELITEK to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue ELITEK in patients developing hemolysis. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior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

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

STUDY 1 (CONT'D)

IN PEDIATRIC PATIENTS, ELITEK RAPIDLY LOWERED URIC ACID AND MAINTAINED NORMAL LEVELS THROUGHOUT TREATMENT[1,2]

Mean (±SE) plasma uric acid concentrations over time for all patients[2]



SE=standard error.

Primary endpoint

- The uric acid $AUC_{0-96\ hr}$ was significantly lower in the ELITEK group (128 ± SE 14 mg/hr/dL) vs the allopurinol group (328 ± SE 26 mg/hr/dL)[1]

All but one patient in the ELITEK arm had reduction and maintenance of uric acid levels to within or below the normal range during the treatment. The incidence of renal dysfunction was similar in the two study arms; one patient in the allopurinol arm developed acute renal failure.[1]

The recommended dose of ELITEK is 0.2 mg/kg as a 30-minute IV infusion daily for up to 5 days. Dosing beyond 5 days or administration of more than one course is not recommended.[1]

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.

ELITEK® rasburicase IV Infusion

STUDY 2

PROPHYLACTIC USE OF ELITEK (rasburicase) WAS STUDIED IN MAJORITY-PEDIATRIC PATIENTS AT HIGH, INTERMEDIATE, AND LOW RISK OF TLS ASSOCIATED WITH HYPERURICEMIA[3]

69%
of patients were at high or intermediate risk at baseline[3]

88%
of pediatric patients had normal uric acid levels (<8 mg/dL) at baseline[3]

Patients meeting at least 1 of the following criteria were enrolled in the trial[3]:

- NHL ≥stage III
- NHL ≥stage II with high tumor burden defined as LDH level twice or more the ULN and/or tumor mass with a diameter ≥10 cm
- ALL or acute non-lymphoid leukemia

Additional eligibility criteria were life expectancy of ≥4 weeks and Karnofsky scale of ≥30% or an ECOG ≤3.[3]

Patients were stratified based on risk levels defined as[3]:

Parameter	Sponsor-defined risk classification at baseline		
	LOW	INTERMEDIATE	HIGH
Baseline WBC† count (x 10^9/L)	≤25 and	All patients not considered to be at low or high risk	>50 and/or
Baseline LDH† (ULN)	≤2 x ULN and		>5 x ULN and/or
Baseline hyperuricemic (uric acid ≥8 mg/dL)	No		Yes

LDH=lactate dehydrogenase; ULN=upper limit of normal.
†Immediately prior to first dose of study drug.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for pediatric ALL: If uric acid >8 mg/dL and/or patient has renal dysfunction or LDH >2 x ULN, rasburicase is strongly recommended if available

In study 1, 27 patients received rasburicase. Of those, 10 were hyperuricemic. LDH in patients with lymphoma=1599±1022 (U/L).
All values are mean ± standard deviation; there were no significant differences comparing baseline values between treatment groups.[2]
NCCN=National Comprehensive Cancer Network.

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 prechilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection.**

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

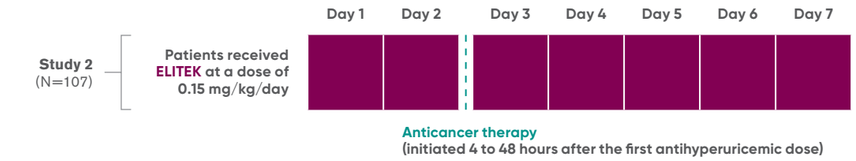
STUDY 2 (CONT'D)

ELITEK MAINTAINED NORMAL URIC ACID LEVELS IN 99% OF PATIENTS RECEIVING 0.15 mg/kg/DAY BY DAY 2[1]

Prophylactic use of ELITEK was studied prior to and concurrent with anticancer therapy[1]

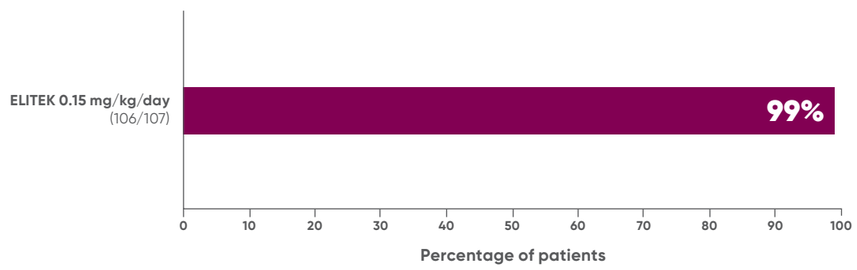
- A multicenter, single-arm study conducted in 107 patients (89 pediatric, 18 adult) with hematologic malignancies at risk for TLS associated with hyperuricemia[1,3]
- **Primary endpoint:** maintenance of uric acid levels ≤6.5 mg/dL (patients <13 years) or ≤7.5 mg/dL (patients ≥13 years) within 48 hours post initiation of ELITEK until 24 hours after last administration without the need for allopurinol or other agents[1]

Pediatric clinical trial design[1,3‡]



‡Actual deviations from study protocol occurred in 2/107 patients (anticancer therapy given prior to first administration of ELITEK); presumed deviations from study protocol occurred in 18/107 patients (anticancer therapy was same as first administration of ELITEK or may have been prior to ELITEK administration).[3]

Pediatric patients maintaining normal uric acid levels (≤6.5 mg/dL for patients <13 years of age or ≤7.5 mg/dL for patients ≥13 years of age) 2 days post initiation of ELITEK without allopurinol or other agents[1]



Primary endpoint

- The proportion of patients with maintenance of uric acid levels (≤6.5 mg/dL for patients <13 years of age or ≤7.5 mg/dL for patients ≥13 years of age) at 48 hours in study 2 was 99% (106/107)[1]

The recommended dose of ELITEK is 0.2 mg/kg as a 30-minute IV infusion daily for up to 5 days. Dosing beyond 5 days or administration of more than one course is not recommended.[1]

Important Safety Information cont'd

CONTRAINDICATIONS

ELITEK is contraindicated in patients with a history of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase. ELITEK is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD).

ELITEK® rasburicase IV Infusion

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

STUDY 3

PROPHYLACTIC USE OF ELITEK (rasburicase) WAS STUDIED IN MAJORITY-PEDIATRIC PATIENTS AT HIGH, INTERMEDIATE, AND LOW RISK OF TLS ASSOCIATED WITH HYPERURICEMIA[3]

69%
of patients were at high risk at baseline[3]

58%
of patients had normal uric acid levels (<8 mg/dL) at baseline[3]

Patients were stratified based on risk levels

Patients meeting at least 1 of the following criteria were enrolled in the trial[3]:

- Small, noncleaved-cell (Burkitt or non-Burkitt) NHL ≥stage III
- B-cell leukemia (of Burkitt type) with L_3 morphology by FAB classification
- ALL with WBC count ≥50,000/mm^3
- ALL without regard to WBC count, but with clinical, radiologic, or laboratory evidence of high tumor burden that, in the opinion of the investigator, would produce significant hyperuricemia during tumor lysis
- Lymphoblastic lymphomas ≥stage III with clinical, radiologic, or laboratory evidence of high tumor burden that, in the opinion of the investigator, would produce significant hyperuricemia during tumor lysis
- Lymphoma or leukemia with a uric acid level of ≥8.0 mg/dL and either creatinine or LDH level at least twice the ULN

Additional eligibility criteria were life expectancy of ≥4 weeks and Karnofsky scale of ≥30% or an ECOG ≤3.[3]

FAB=French-American-British.

Patients were stratified based on risk levels defined as[3]:

Parameter	Sponsor-defined risk classification at baseline		
	LOW	INTERMEDIATE	HIGH
Baseline WBC[§] count (x10^9/L)	≤25 and	All patients not considered to be at low or high risk	>50 and/or
Baseline LDH[§] (ULN)	≤2 x ULN and		>5 x ULN and/or
Baseline hyperuricemic (uric acid ≥8 mg/dL)	No		Yes

[§]Immediately prior to first dose of study drug.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Consider prophylactic rasburicase in patients with high WBC count prior to starting therapy even if uric acid <8 mg/dL[5]

In study 1, 27 patients received rasburicase. Of those, 17 were nonhyperuricemic. In patients with leukemia, WBC=83.2±81.0 (10^9/L). All values are mean ± standard deviation; there were no significant differences comparing baseline values between treatment groups.[2]

Important Safety Information cont'd

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20%), when used concomitantly with anticancer therapy, are vomiting, nausea, fever, peripheral edema, anxiety, headache, abdominal pain, constipation, diarrhea, hypophosphatemia, pharyngolaryngeal pain, and increased alanine aminotransferase.

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

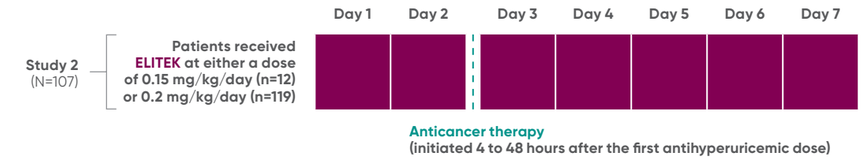
STUDY 3 (CONT'D)

ELITEK MAINTAINED NORMAL URIC ACID LEVELS IN 92% OF PATIENTS RECEIVING 0.15 mg/kg/DAY AND 95% OF PATIENTS RECEIVING 0.2 mg/kg/DAY BY DAY 2[1]

Prophylactic use of ELITEK was studied prior to and concurrent with anticancer therapy[1]

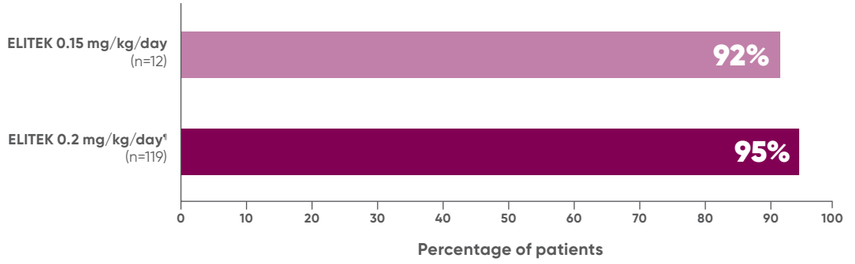
- A multicenter, single-arm study conducted in 131 patients (130 pediatric, 1 adult) with hematologic malignancies at risk for TLS associated with hyperuricemia[1,3]
- **Primary endpoint:** maintenance of uric acid levels ≤6.5 mg/dL (patients <13 years) or ≤7.5 mg/dL (patients ≥13 years) within 48 hours post initiation of ELITEK until 24 hours after last administration without the need for allopurinol or other agents[1]

Pediatric clinical trial design[1,3‖]



‖Actual deviations from study protocol occurred in 3/131 patients (anticancer therapy given prior to first administration of ELITEK); presumed deviations from study protocol occurred in 13/131 patients (anticancer therapy was same as first administration of ELITEK or may have been prior to ELITEK administration).[3]

Pediatric patients maintaining normal uric acid levels (≤6.5 mg/dL for patients <13 years of age or ≤7.5 mg/dL for patients ≥13 years of age) 2 days post initiation of ELITEK without the need for allopurinol or other agents[1]



Primary endpoint

- The proportion of patients with maintenance of uric acid levels (≤6.5 mg/dL for patients <13 years of age or ≤7.5 mg/dL for patients ≥13 years of age) at 48 hours in study 2 was 92% in the 0.15-mg/kg group (n=12 and 95% in the 0.2-mg/kg group (n=119)[1]

Recommended dose: 0.2 mg/kg as a 30-minute IV infusion daily for up to 5 days. Dosing beyond 5 days or administration of more than one course is not recommended.[4]

Important Safety Information cont'd

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Consider the benefits and risks of ELITEK and possible risks to the fetus when prescribing ELITEK to a pregnant woman.
- **Lactation:** Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with ELITEK and for 2 weeks after the last dose.

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

ELITEK® rasburicase IV Infusion

ELITEK HAS A PROVEN SAFETY PROFILE

The data below reflect exposure to ELITEK in 265 pediatric and 82 adult patients enrolled in one active-controlled trial (study 1), two uncontrolled trials (studies 2 and 3), and an uncontrolled safety trial (n=82). Additional data were obtained from an expanded access program of 356 patients, for whom data collection was limited to serious adverse reactions. Among these 703 patients, the median age was 10 years (range=10 days to 88 years). Other patient characteristics were as follow:

CHARACTERISTIC	% OF PATIENTS
Sex	
Male	63
Female	37
Race	
Caucasian	73
African	9
Asian	4
Other/unknown	14

Among the 347 patients for whom all adverse reactions, regardless of severity, were assessed, the most frequently observed adverse reactions (incidence ≥10%) were:

ADVERSE REACTION	% OF PATIENTS
Vomiting	50
Fever	46
Nausea	27
Headache	26
Abdominal pain	20
Constipation	20
Diarrhea	20
Mucositis	15
Rash	13

In study 1, an active-controlled study, the following adverse reactions occurred more frequently in ELITEK-treated subjects than allopurinol-treated subjects: vomiting, fever, nausea, diarrhea, and headache. Although the incidence of rash was similar in the 2 arms, severe rash was reported in only 1 ELITEK-treated patient.

Important Safety Information cont'd

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.**
- **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 prechilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection.**

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

References: 1. ELITEK [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** Goldman SC et al. *Blood.* 2001;97:2998-3003. **3.** Data on file. Bridgewater, NJ: sanofi-aventis U.S. LLC. **4.** Ueng S. *Proc Bayl Univ Med Cent.* 2005;18(3):275-279. **5.** National Comprehensive Cancer Network. NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia. V1.2020. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Updated May 30, 2019. Accessed August 19, 2019.

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