Example Clinical Protocol for Rasburicase (Elitek®) Use

Situation[1]: Rasburicase is the only recombinant urate oxidase FDA-approved for the initial management of uric acid in patients with leukemia, lymphoma, and solid tumors who are receiving anticancer therapy. It was studied in patients at high or intermediate (potential) risk of developing Tumor Lysis Syndrome (TLS) associated with hyperuricemia.

Background[1,2]: Prophylactic use of rasburicase was studied in a randomized, multicenter, open label, phase 3 trial (n=275) where rasburicase 0.2 mg/kg/day monotherapy vs rasburicase (days 1-3) + allopurinol (days 3-5) vs allopurinol 300 mg/day monotherapy were initiated prior to anticancer therapy. The primary endpoint of the study was response rate defined as the proportion of patients with plasmic uric acid levels maintained at ≤7.5 mg/dL between 3-7 days after initiation of antihyperuricemic treatment. Patients enrolled in the trial were are at high or intermediate (potential) risk of hyperuricemia and tumor lysis syndrome.

Results[2]: Rasburicase administered prophylactically maintained normal uric acid levels (≤7.5 mg/dL) in significantly more high risk patients (89%, n=82) vs allopurinol (68%, n=85) between 3-7 days after initiation of antihyperuricemic treatment (P=0.001). These results were consistent with the overall study population (**primary endpoint**): 87% (n=92) of high and intermediate (potential) risk patients receiving rasburicase vs 66% (n=91) with allopurinol (P=0.001).

Recommendations: See below.

Indication[1]

- Rasburicase 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.
- Rasburicase is indicated only for a single course of treatment.

Criteria for Use

Criteria for risk level of patients in the phase 3 trial:

High Risk[2-4]	**Intermediate (Potential) Risk**[2]
Aggressive leukemia or lymphoma (defined by REAL) including CLL, Anaplastic Large Cell Lymphoma, Burkitt Lymphoma, Diffuse Large B-cell Lymphoma (DLBCL), Lymphoblastic lymphoma, Peripheral T-cell lymphoma	Other aggressive lymphomas/leukemias not meeting REAL criteria with LDH ≥2X ULN
Acute Myeloid Leukemia (AML)	Any stage III or IV lymphoma or leukemia
Plasma Uric Acid >7.5 mg/ dL	Bulky lymph node/tumor (> 5cm) in stage I or II disease
High-grade myelodysplastic syndrome (MDS) with >10% bone marrow blast involvement	
Chronic Myeloid Leukemia (CML) in blast crisis	

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

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Important Safety Information, cont'd

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

- **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.**

Dosing and Administration[1]

Administer rasburicase once daily for up to 5 days.

First Dose:

- 0.2 mg/kg, infuse over 30 minutes
- Rasburicase must be reconstituted with the diluent provided in the carton. Reconstitute the 1.5 mg vial of rasburicase with 1 mL diluent OR 7.5 mg vial of rasburicase with 5 mL of diluent. Mix by swirling gently
- **Administer rasburicase as an intravenous infusion only**
- Inject calculated dose of reconstituted rasburicase solution into infusion bag containing appropriate volume of 0.9% sterile sodium chloride to achieve total volume of 50 mL
- Infuse over 30 minutes through a separate line or flush line with at least 15mL of normal saline prior to and after rasburicase infusion
- Do not use filters during infusion of reconstituted rasburicase drug product

May Repeat Dose:

- Not indicated for dosing beyond 5 days or administration of more than 1 course

Note: 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

Anti-Cancer Therapy Considerations

Agents used to treat leukemia or lymphoma associated with elevated uric acid or TLS due to elevated uric acid include:[5-19]*

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

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

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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.** 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 of tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone – results on a multicenter phase III study. *J Clin Oncol.* 2010;28(27):4207-4213. **3.** Jakic-Razumovic J, Aurer I. The World Health Organization classification of lymphomas. *Croat Med J.* 2002; 43(5): 527-534. **4.** Nicolaides C, Dimou S, Pavlidis N. Prognostic factors in aggressive non-Hodgkin's lymphomas. *Oncologist.* 1998; 3(3): 189-197. **5.** Belay Y, et al. *J Oncol.* 2017, Article ID 9684909. https://doi.org/10.1155/2017/9684909 **6.** Adriamycin [prescribing information]. Bedford, OH: Bedford Laboratories; 2006 **7.** Marqibo [prescribing information]. South San Francisco, CA: Talon Therapeutics; 2012. **8.** Pomalyst [prescribing information]. Summit, NJ: Celgene Corporation; 2016 **9.** Bose P, et al. J Clin Pharm Ther. 2011;36(3):299-326. **10.** Gazyva [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2016. **11.** Kyprolis [prescribing information]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc.; 2017. **12.** Ninlaro [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2016. **13.** Sprycel [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015. **14.** Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018. **15.** Synribo [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc; 2015. **16.** Treanda [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2015. **17.** Venclexta [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; 2018. **18.** Istodax [prescribing information]. Summit, NJ: Celgene Corporation; 2016. **19.** Adcetris [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; 2016.