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Subject: Rasburicase (Elitek®)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

<u>Dosage/</u> <u>Administration</u>	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	<u>Definitions</u>
Related Guidelines	<u>Other</u>	References	<u>Updates</u>		

DESCRIPTION:

Rasburicase (Elitek) is a recombinant urate oxidase produced by a genetically modified *Saccharomyces cerevisiae* strain. In humans, uric acid is the end product in the catabolic pathway of purines (most abundantly found in DNA), which is then primarily excreted by the kidneys. Urate oxidase catalyzes the oxidation of uric acid into the inactive and more soluble metabolite allantoin. Urate oxidase is found in most mammals but not humans. Rasburicase was first approved by the FDA in July 2002 for "the initial management of plasma uric acid levels in pediatric 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." The indication was expanded in October 2009 to include adult patients. Elitek was previously granted an orphan drug designation for "the treatment of malignancy-associated or chemotherapy-induced hyperuricemia" in October 2000.

Tumor lysis syndrome (TLS) consists of metabolic abnormalities caused by the rapid destruction of tumor cells and subsequent release of intracellular components. The syndrome is characterized by hyperuricemia and electrolyte abnormalities (i.e., hyperkalemia, hyperphosphatemia, hypocalcemia) and may lead to acute renal failure, arrhythmias, and/or death. Symptoms generally occur 12 to 72 hours after, but may occur prior to, initiation of chemotherapy. The malignancies most often associated with TLS include those with large tumor burden, rapid cell proliferation, and high sensitivity to chemotherapy. Large tumor burden for hematological malignancy is indicated by high white blood cell counts (WBCs) and elevated lactate dehydrogenase [i.e., >2X the upper limit of normal (ULN)]. Other risk factors include advanced age, preexisting renal dysfunction, and elevated baseline serum uric acid levels.

The most current consensus guidelines for the management of TLS were published by the British Committee for Standards in Hematology in 2015. The guidelines recommend up to 7 days of allopurinol prophylaxis along with increased hydration post-initiation of treatment for "intermediate risk" patients, and

recommend prophylaxis with rasburicase along with increased hydration for "high risk" patients. In high-risk adults, without established clinical or laboratory TLS, the guidelines state that TLS can be prevented in the majority of patients using a single fixed dose of 3 mg of rasburicase, but patients must be followed by careful monitoring with repeat dosing if required. In high-risk children, a single dose of rasburicase 0.2 mg/kg is recommended, as current evidence is too limited to recommend a fixed 3 mg dose. For treatment of established TLS in adults and children the guidelines recommend a dose of 0.2 mg/kg/day with the length of treatment determined by clinical response. Combined use of allopurinol and rasburicase is NOT recommended as it may reduce the effectiveness of rasburicase. The National Comprehensive Cancer Network (NCCN) recommends to the use of rasburicase in patients with certain high-risk features, and state that one dose of 3 to 6 mg is frequently adequate. Redosing should be individualized.

In order to gain FDA approval, rasburicase was investigated in three studies (1 RCT and 2 single-arm studies) totaling 265 patients with acute leukemia or non-Hodgkin's lymphoma. The population was largely limited to pediatric patients (246 of 265). Rasburicase was administered as a 30-minute infusion once (n=251) or twice (n=14) daily at a dose of 0.15 or 0.2 mg/kg/dose (total daily dose 0.2 to 0.4 mg/kg/day). In a pooled analysis among patients with pre-treatment uric acid ≥8 mg/dL (baseline median 10.6 mg/dL) the median per-patient change in plasma uric acid concentration by 4 hours after the first dose was a decrease of 9.1 mg/dL. Among the patients with a pre-treatment plasma uric acid level <8 mg/dL (baseline median 4.6 mg/dL), the median per-patient change in plasma uric acid concentration was a decrease of 4.1 mg/dL. Plasma uric acid concentration was maintained by 4 hours for 92%, by 24 hours for 93%, by 48 hours for 97%, by 72 hours for 99%, and by 96 hours for 100% of patients.

Rasburicase was also investigated in five studies [1 RCT (n=275) and 4 uncontrolled studies] totaling 342 adults with leukemia, lymphoma, or other hematologic malignancy. In the open-label RCT, patients at risk for hyperuricemia and TLS received at least one dose of study drug. The median age was 56 years, 62% were males, 80% were Caucasian, 66% had leukemia, 29% had lymphoma, and 18% were hyperuricemic (uric acid ≥7.5 mg/dL) at study entry. Patients in Arm A received rasburicase 0.2 mg/kg/day IV for 5 days, Arm B received rasburicase from day 1 through day 3 followed by oral allopurinol 300 mg once a day from day 3 through day 5 (overlap on day 3), and Arm C received oral allopurinol for 5 days. The major endpoint of this study was the uric acid response rate defined as the proportion of patients with plasma uric acid levels ≤7.5 mg/dL from day 3 to day 7, after initiation of antihyperuricemic treatment. The response rates were, 87% (Arm A), 78% (Arm B), and 66% (Arm C). The response rate in arm A was significantly greater than in arm C (p<0.001), but not for Arm B compared to Arm C. There was no difference in clinical TLS at 3%, 3%, and 4% for Arms A, B, and C, respectively.

A 2013 meta-analysis by Feng et al. examined the effectiveness of a single fixed dose of rasburicase across 10 studies (8 retrospective and 2 prospective) that evaluated adults at high risk of TLS. A comparison was made using the results from patients treated with rasburicase at the FDA-approved dosage of 0.2 mg/kg for 5 day or patients treated with allopurinol. The pool data showed that the single dose was as effective as the prolonged treatment in the control of uric acid levels, and superior to allopurinol. The authors concluded that the data suggest that single-dose rasburicase is clinically effective and cost efficient for the prophylaxis of high-risk TLS and the treatment of hyperuricemia in adult patients with cancer. A 2017 meta-analysis by Yu et al. explored the optimal single-dose regimen. The authors concluded that "for adult patients, a single 6 mg rasburicase dose is sufficient to normalize and sustain lower uric acid and creatinine levels in adults with TLS. This dose, therefore, balances cost and efficacy of treatment. The 3- and 4-5-mg single dose can be considered if the baseline uric acid level <12 mg/dL, with close monitoring of clinical and biochemical parameters, and repeat dosing if required."

POSITION STATEMENT:

Initiation of rasburicase (Elitek) **meets the definition of medical necessity** when a member has an indication listed in **Table 1**, and the associated criteria for use and maximum allowable dosage limits are met:

TABLE 1

Indication	Criteria for Use	Maximum Allowable Dosage
Prevention of TLS in members with high-risk cancers	 ALL of the following ("1" and "2"): 1. Member has ANY of following high-risk cancers: a. ALL with WBC ≥100,000/mcL and/or serum LDH ≥2-times ULN b. AML with WBC ≥100,000/mcL c. Burkitt lymphoma/leukemia d. Lymphoblastic lymphoma e. Diffuse large B-cell lymphoma with a serum LDH ≥2-times ULN f. Non-indolent or aggressive* NHL (including subtypes) with both bulky tumor mass (>10 cm in adults) and serum LDH ≥ULN g. Any cancer with renal involvement by the tumor 2. Member will receive chemotherapy for their cancer within 24 hrs following rasburicase administration 	Adults: 6 mg X 1 dose (if the baseline serum uric acid level is 12 mg/dL or greater), OR 3 mg X 1 dose (if the baseline serum uric acid level is less than 12 mg/dL or unknown) within 24 hours before initiation of chemotherapy. Repeat doses of 3 mg can be given, up to 5 days following the initial dose of rasburicase, for any follow-up serum uric acid levels ≥7.5 mg/dL [†] . Children (<18 years of age): 0.2 mg/kg X 1 dose within 24 hours before initiation of chemotherapy. Repeat doses of 0.2 mg/kg can be given, up to 5 days following the initial dose of rasburicase, for any follow-up serum uric acid levels ≥7.5 mg/dL [†] .
Prevention of TLS in members with moderate-risk cancers	 ALL of the following ("1", "2", and "3"): 1. Member has ANY of following moderate-risk cancers: a. ALL with WBC <100,000/mcL and serum LDH <2-times ULN b. AML with WBC ≥25,000/mcL to <100,000/mcL and/or serum LDH ≥2-times ULN 	Adults: 6 mg X 1 dose (if the baseline serum uric acid level is 12 mg/dL or greater), OR 3 mg X 1 dose (if the baseline serum uric acid level is less than 12 mg/dL or unknown) within 24 hours before initiation of chemotherapy. Repeat

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		C.	treat	with either WBC ≥50,000/mcL or ed with targeted or biological apies (i.e., fludarabine or rituximab)	doses of 3 mg can be given, up to 5 days following the initial dose of
		d.	Gerr	n cell cancer	rasburicase, for any follow-
		e.	Neu	roblastoma	up serum uric acid levels
		f.	(inclutumo	indolent or aggressive* NHL uding subtypes) with either bulky or mass (>10 cm in adults) or serum ≥ULN	≥7.5 mg/dL [†] . Children (<18 years of
	2.	At	least (ONE of the following ("a" or "b"):	age): 0.2 mg/kg X 1 dose
		a.	allop	aber is not a suitable candidate for urinol prophylaxis due to at least ONE ollowing ("i" or "ii"):	within 24 hours before initiation of chemotherapy. Repeat doses of 0.2 mg/kg
			i.	Member has a hypersensitivity to allopurinol	can be given, up to 5 days following the initial dose of rasburicase, for any follow-
			ii.	Member requires urgent treatment of their cancer that cannot be delayed more than 48 hours	up serum uric acid levels ≥7.5 mg/dL [†] .
		b.		ber has ONE or more of the following tional TLS risk factors ("i", "ii", or "iii"):	
			i.	Adequate hydration of the member is difficult or not possible (e.g., comorbid heart failure)	
			ii.	Member has pre-existing renal impairment (i.e., CrCl <60 mL/min) or acute renal failure	
			iii.	Member has a baseline serum uric acid level >ULN	
	3.	car		will receive chemotherapy for their within 24 hrs following rasburicase ration	
Treatment of members with documented laboratory or clinical TLS		The member meets the Cairo-Bishop definition of laboratory or clinical TLS			0.2 mg/kg/day for a maximum of 5 days. An additional dose of up to 0.2 mg/kg can be given per day (i.e., two total doses per day on days 0 to 5) if a follow-up serum uric acid level is ≥7.5 mg/dL† up to 5 days after the initial dose of rasburicase.

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CLL = chronic lymphocytic leukemia,

CrCl = creatinine clearance, LDH = lactate dehydrogenase, NHL= non-Hodgkin lymphoma,

TLS = tumor lysis syndrome, ULN = upper limit of normal, WBC = white blood cells

*The NHLs that are classified as indolent (i.e., slow-growing or low grade) are marginal zone, nodal marginal zone B-cell, lymphoplasmacytic, peripheral T-cell, and follicular cell lymphomas; and Mycosis fungoides.

[†]Serum uric acid should be measured at least 4 hours after the administration of rasburicase. It is recommended that uric acid be evaluated every 6 to 12 hours until levels are normalized.

Duration of Approval: 1 month

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For initial management of plasma uric acid levels in pediatric (≥1 month) 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.
- Administer at 0.2 mg/kg as an intravenous (IV) infusion over 30 minutes daily for up to 5 days.
- Dosing beyond 5 days or administration of more than one course is **NOT** recommended.
- Do NOT administer as an IV bolus.

Dose Adjustments

No dosage adjustment is needed for members with renal or hepatic impairment.

Drug Availability

- 1.5 mg powder per single-use vial.
- 7.5 mg powder per single-use vial.
- Must be reconstituted with the diluent provided in the carton.
- The lyophilized drug product and the diluent for reconstitution should be stored at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

PRECAUTIONS:

Boxed Warnings

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

- Hypersensitivity Reactions Rasburicase can cause severe hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue in patients who experience a serious hypersensitivity reaction.
- Hemolysis Do not administer to patients with glucose-6-phosphate dehydrogenase (G6PD)
 deficiency. Immediately and permanently discontinue in patients developing hemolysis. Screen
 patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry)
 prior to starting
- **Methemoglobinemia** Rasburicase can result in methemoglobinemia in some patients. Immediately and permanently discontinue in patients developing methemoglobinemia.
- Interference with Uric Acid Measurements Rasburicase 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.

Contraindications

- History of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase
- Individuals deficient in glucose-6-phosphate dehydrogenase (G6PD)

Precautions/Warnings

- See Boxed Warnings
- **Pregnancy Category C** There are no studies of rasburicase in pregnant women. Because of the observed teratogenic effects of rasburicase in animal reproductive studies, use rasburicase during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J2783	Injection, rasburicase, 0.5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C56.1 – C56.9	Malignant neoplasm of ovary
C62.00 - C62.92	Malignant neoplasm of testis
C74.00 - C74.92	Malignant neoplasm of adrenal gland
C83.00 - C83.99	Non-follicular lymphoma
C84.60 - C84.69	Anaplastic large cell lymphoma, ALK-positive
C84.70 – C84.7A	Anaplastic large cell lymphoma, ALK-negative
C85.10 - C85.89	Other specified types of non-Hodgkin lymphoma
C91.00 - C91.92	Lymphoid leukemia
C92.00 - C92.02	Acute myeloblastic leukemia
C92.40 - C92.42	Acute promyelocytic leukemia
C92.50 - C92.52	Acute myelomonocytic leukemia

C92.60 - C92.62	Acute myeloid leukemia with 11q23-abnormality
C92.A0 – C92.A2	Acute myeloid leukemia with multilineage dysplasia
C93.00 - C93.02	Acute monoblastic/monocytic leukemia
C95.00 - C95.02	Acute leukemia of unspecified cell type
E79.0	Hyperuricemia without signs of inflammatory arthritis and tophaceous disease
E88.3	Tumor lysis syndrome

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Clinical TLS: presence of laboratory TLS and any <u>one</u> of the following clinical manifestations when not directly or probably attributable to a therapeutic agent: (1) serum creatinine level ≥1.5-times the institutional upper limit of normal (UNL) (age >12 or age-adjusted), (2) cardiac arrhythmia, (3) sudden death, or (4) seizure.

Laboratory TLS: see Cairo-Bishop definition in the "Other" section

Tumor Lysis Syndrome (TLS): a life-threatening complication that arises when the rapid destruction of tumor cells releases excessive quantities of cellular contents into the systemic circulation resulting in a metabolic disturbance characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. This metabolic derangement may lead to acute renal failure and cardiac arrhythmias. It can be classified as laboratory TLS (no clinical manifestations) or clinical TLS (patients with life-threatening clinical abnormalities).

RELATED GUIDELINES:

None

OTHER:

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Lab Measurement	Criteria
Uric acid	≥8 mg/dL or 25% increase from baseline
Potassium	≥6 mEq/L or 25% increase from baseline

Phosphorous	≥1.45 mmol/L or 25% increase from baseline (adults), or ≥2.1 mmol/L or	
	25% increase from baseline (children)	
Calcium	≤1.75 mmol/L or 25% decrease from baseline	
The presence of two or more of the above abnormalities in a patient with cancer or within 3 days before		
or 7 days after initiation of chemotherapy.		

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 08/08/18.

GUIDELINE UPDATE INFORMATION:

10/15/15	New Medical Coverage Guideline.
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Revision to guideline consisting of updated dosage in position statement.
10/15/16	Review and revision to guideline consisting of updating the description, position statement, and references.
09/15/17	Review and revision to guideline consisting of updating the description, position statement, and references.
09/15/18	Review and revision to guideline consisting of updating the precautions section and references.
10/01/21	Revision: New ICD-10 code C84.7A added.