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Policy Number: 048.002 **Title: Coverage Determination Policy for Elitek (Rasburicase)**		

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Approved by: Vincent F Huerta Jr, MD, CHCQM Senior Medical Director	Vincent F Huerta Jr, MD, CHCQM Digitally signed by Vincent F Huerta Jr, MD, CHCQM Date: 2023.08.16 18:24:35 -05'00'	**Date:** 08/16/23
Reviewed by: Pathik Tripathi, Pharm.D, MS Director, Clinical Pharmacy	Pathik Tripathi Digitally signed by Pathik Tripathi Date: 2023.08.17 11:29:28 -05'00'	**Date:** 08/16/23

Available LCD/NCD/LCA: None

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Title: Coverage Determination Policy for Elitek (Rasburicase)

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Coverage Policy Number: 048.002

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

ALL of the following criteria must be met in addition to any indication-specific criteria:

- Patient does not have Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Patient is currently receiving anti-cancer therapy
- Dosing is in accordance with the United States Food and Drug Administration approved labeling and established guidelines as outlined in the dosing table

WellMed Medical Management will cover **Elitek (Rasburicase)** as medically necessary for the following:

1. **Prevention of tumor lysis syndrome (TLS)** when **ONE** the following criteria are met:
   - **A.** Patient is at high risk for developing TLS as determined by ONE of the following:

     ALL with WBC ≥100,000/mcL and/or serum LDH ≥2-times ULN

     i. Burkitt lymphoma/leukemia

     ii. Diffuse large B-cell lymphoma with a serum LDH ≥2-times ULN

     iii. Lymphoblastic lymphoma

     iv. AML with WBC ≥100,000/mcL

     v. Any cancer with renal involvement by the tumor

     vi. Aggressive NHLs (including subtypes) with both bulky tumor mass (>10 cm in adults) and serum LDH ≥ULN

OR

   - **B.** Patient is at intermediate risk* for developing TLS with renal dysfunction or is allergic to allopurinol

2. **Treatment of TLS** as determined by **ONE** of the following criteria:

   A. **Laboratory TLS** as evidenced by **2 or more** of the following abnormalities within 3 days before and up to 7 days after initiation of treatment in a patient with cancer or undergoing treatment for cancer:

      i. Uric acid: 476 mmol/L (8 mg/dL) or higher or 25% increase from baseline
      ii. Potassium: 6 mmol/L (6 mEq/L) or higher or 25% increase from baseline
      iii. Phosphate (Adults): 1.45 mmol/L (4.5 mg/dL) or higher or 25% increase from baseline
      iv. Phosphate (Pediatrics): 2.1 mmol/L (6.5 mg/dL) or higher or 25% increase from baseline
      v. Calcium: 1.75 mmol/L (7 mg/dL) or less or 25% decrease from baseline

OR

   B. **Clinical TLS** as defined by patients with laboratory TLS and at least ONE of the following findings:

      i. Creatinine: 1.5 or greater x ULN or higher (older than 12 years or age-adjusted)
      ii. Cardiac arrhythmia
      iii. Seizure
      iv. Any clinical setting of highly proliferative malignancy/highly treatment sensitive tumor expected to result in TLS following initiation of therapy

Note: Other clinical concerns will be decided on case-by-case basis per oncology MDR

****Intermediate-Risk Disease: Stage I/II and LDH <2X ULN***

FDA Approved Dose and Indication

FDA-approved Dose:

- 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.
- Prophylaxis or treatment (multidose weight-based): 0.2 mg/kg IV infusion over 30 minutes daily for up to 5 days (FDA dosage)
- Dosing beyond 5 days or administration of more than one course is NOT recommended.
- Do NOT administer as an IV bolus
- Prophylaxis of high-risk patients (single fixed-dose), 3 mg IV followed by careful monitoring; repeat dose if necessary (guideline dosage)
- Treatment of established tumor lysis syndrome (weight-based), 0.2 mg/kg/day IV as a 30 minute infusion with duration determined by clinical response (guideline dosage)
- Prophylaxis or treatment (single dose), 6 mg IV once or 0.15 mg/kg IV; may consider single doses of 3 or 4.5 mg if baseline uric acid level is less than 12 mg/dL, with monitoring and repeat dosing if required (off-label dosage)

Dose Adjustments:

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

General Background

Black Box Warning:

Hypersensitivity reactions: Elitek can cause severe hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue Elitek therapy 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 pre-chilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection.

Elitek (Rasburicase) 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. Centerpiece of treatment includes vigorous hydration, management of hyperuricemia and frequent monitoring of electrolytes and aggressive correction (essential). Allopurinol or febuxostat are recommended for patients with low-risk or intermediate-risk disease. Rasburicase is recommended for intermediate-risk disease (if renal dysfunction and uric acid, potassium, and/or phosphate greater than ULN) or high-risk disease.

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.

Clinical Evidence

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 <8mg/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 hour 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 342adults 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 hyperuricemia (uric acid ≥7.5 g/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.

HCPCS Code

HCPCS Code	Drug Description
J2783	injection, Elitek (Rasburicase), 0.5mg

Acronyms

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

G6PD = Glucose-6-Phosphate Dehydrogenase

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Policy History/Revision Information

Date Revised	Type of Changes (Significant or Minor)	List Significant Changes and/or Status of policy
02/01/19	Significant	New drug criteria created for Elitek (Rasburicase)-Eric McDermott, PharmD.
02/18/22	Minor	Criteria updated per new template, added hyperlinks, HCPCS code. Added options of any clinical setting of sensitive tumor with high risk of TLS & determination will be made on case by case basis under unusual circumstances – Brent Bryant, PharmD
08/02/23	Minor	Annual criteria revision. Defined “intermediate risk” per NCCN. Mira Dawood, PharmD