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PHARMACY / MEDICAL POLICY – 5.01.632

Pharmacologic Treatment of Bladder Cancer

Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 24, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES |HISTORY

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Introduction

Bladder cancer occurs in the urinary system, with abnormal tissue developing in the lining of the bladder. Urothelial bladder cancer is the most common type of bladder cancer. Most new urothelial bladder cancers are considered non-muscle invasive. Treatment of bladder cancer depends on the tumor stage, tumor size, and other factors. Depending on how severe the cancer is, treatment options may include chemotherapy, radiation, surgery, or immunotherapy. This policy discusses when the use of certain bladder cancer agents may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Adstiladrin (nadofaragene firadenovec-vncg) Intravesical	**Adstiladrin (nadofaragene firadenovec-vncg) may be considered medically necessary for treatment of non-muscle**

Drug	Medical Necessity

	invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) in adults when the following criteria are met:
	• The individual is aged 18 years and older
	AND
	• Is ineligible for or has elected not to undergo a cystectomy
	AND
	• Has Bacillus Calmette-Guérin (BCG)-unresponsive disease defined as ONE of the following:
	  ○ Persistent or recurrent disease following BCG therapy
	  OR
	  ○ T1 disease following a single induction course of BCG
	AND
	• Has an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less
	AND
	• Dose is limited to 75 mL once every 3 months

Anktiva (nogapendekin alfa inbakicept-pmln) Intravesical	**Anktiva (nogapendekin alfa inbakicept-pmln) may be considered medically necessary for treatment of non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) in adults when the following criteria are met:** • The individual is aged 18 years and older **AND** • Has had a complete resection of high-grade Ta and/or T1 disease after transurethral resection of bladder tumor (TURBT) **AND** • Has histologic confirmation of Bacillus Calmette-Guérin (BCG)-unresponsive CIS without residual high-grade Ta or T1 disease OR with completely resected Ta or T1 disease **AND** • Has received adequate[a] intravesical BCG therapy within the last 12 months **AND** • Has an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less **AND**

Drug	Medical Necessity
	• Documentation of a valid medical rationale is provided for why the individual is not able to use Adstiladrin (nadofaragene firadenovec-vncg) or Keytruda (pembrolizumab) [a]**Note:** Adequate intravesical BCG therapy is defined as administration of at least five of six doses of an initial induction course AND at least two of three doses of maintenance therapy OR at least two of six doses of a second induction course.

Drug	Investigational
Adstiladrin (nadofaragene firadenovec-vncg), Anktiva (nogapendekin alfa inbakicept-pmln)	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of Adstiladrin (nadofaragene firadenovec-vncg) and Anktiva (nogapendekin alfa inbakicept-pmln) not outlined in this policy are considered investigational.**

Approval	Criteria
Length of Approval	
Initial authorization	**Non-formulary exception reviews for Adstiladrin (nadofaragene firadenovec-vncg) and Anktiva (nogapendekin alfa inbakicept-pmln) may be approved for up to 12 months.** **All other reviews for Adstiladrin (nadofaragene firadenovec-vncg) and Anktiva (nogapendekin alfa inbakicept-pmln) may be approved for up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for Adstiladrin (nadofaragene firadenovec-vncg) and Anktiva (nogapendekin alfa inbakicept-pmln) may be approved for up to 12 months if the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
C9169	Injection, nogapendekin alfa inbakicept-pmln, for intravesical use, 1 microgram (used to report Anktiva) (Code terminated 01/01/25)
J9028	Injection, nogapendekin alfa inbakicept-pmln, for intravesical use (Anktiva),1 microgram (new code effective 01/01/25)
J9029	Injection, nadofaragene firadenovec-vncg (Adstiladrin), per therapeutic dose

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

Adstiladrin (nadofaragene firadenovec-vncg) and Anktiva (nogapendekin alfa inbakicept-pmln) are managed through the medical benefit.

Evidence Review

Summary of Evidence

Adstiladrin (nadofaragene firadenovec-vncg)

Adstiladrin (nadofaragene firadenovec-vncg) is a nonreplicating recombinant adenovirus that acts as a gene therapy. The adenovirus delivers the human interferon alfa-2b (IFNα2b) gene to the individual's bladder urothelial cells. Intravesical instillation of Adstiladrin results in cell transduction and transient local expression of the IFNα2b protein that is anticipated to have anti-tumor effects. The safety and effectiveness of Adstiladrin was evaluated in the Phase 3 CS-003 trial (NCT02773849), an open-label, multicenter, single-arm study that enrolled a total of 157 adult individuals with Bacillus Calmette-Guérin (BCG)-unresponsive, high-risk non-muscle invasive bladder cancer (NMIBC) following transurethral resection. Among these, 103 individuals had carcinoma in situ (CIS) with or without papillary tumors, of which 98 were considered evaluable for response. Adstiladrin was administered directly into the individual's bladder by instillation once every 3 months. The trial met its primary endpoint, with more than half (51%) of the 98 evaluable individuals (95% confidence interval [CI], 41 to 61) with CIS with or without concomitant high-grade Ta or T1 disease (CIS ± Ta/T1) achieving a complete response (CR), all by 3 months. Of the individuals who achieved an initial CR, 46% (n = 23 of 50) continued to remain free of high-grade recurrence at 12 months. Safety analyses were done in all individuals who received at least one dose of treatment. Serious adverse reactions (SARs) occurred in 11% of individuals who received Adstiladrin. SARs occurring in >1% of individuals included coronary artery disease and hematuria (blood in urine). Permanent discontinuation of Adstiladrin due to an adverse reaction (AR) occurred in 3 individuals (1.9%). ARs that resulted in permanent discontinuation included bladder spasm instillation site discharge and benign neoplasm of the bladder. Dosage interruptions of Adstiladrin due to an AR occurred in 54 (34%) individuals. ARs in >10% of individuals that required dosage interruption included instillation site discharge, bladder spasm, and micturition (urination) urgency. The most common (>10%) ARs, including laboratory abnormalities (>15%), were increased glucose, instillation site discharge, increased triglycerides, fatigue, bladder spasm, micturition urgency, increased creatinine, hematuria, phosphate decreased, chills, dysuria, and pyrexia (fever).

Anktiva (nogapendekin alfa inbakicept-pmln)

Anktiva (nogapendekin alfa inbakicept-pmln) was evaluated in QUILT-3.032 (NCT03022825), a Phase 2/3 single-arm, multicenter trial that included 77 efficacy-evaluable adults with BCG-unresponsive, high-risk NMIBC CIS with or without Ta/T1 papillary disease following transurethral resection. BCG-unresponsive, high-risk NMIBC CIS was defined as persistent or

recurrent CIS alone or with Ta/T1 disease within 12 months of completion of adequate BCG therapy. Adequate BCG therapy was defined as administration of at least five of six doses of an initial induction course plus either of at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all individuals with Ta or T1 disease had undergone TURBT to remove all resectable disease. Residual CIS not amenable to complete resection, fulguration, or cauterization was permitted. The safety of Anktiva with BCG was evaluated in Cohort A (n = 88) of QUILT-3.032. The median number of doses of Anktiva with BCG administered to individuals was 12 (range: 2 to 30) doses. The median duration of exposure to Anktiva with BCG was 7.1 months (range: 0.26 to 36.3 months). The CR rate was 62%, with the upper end of the 95% confidence interval (CI) being 73%. The duration of response (DOR), as of the November 2023 cut-off, was more than 47 months and ongoing. The prolonged DOR beyond 24 months with Anktiva/BCG exceeds the benchmark for the magnitude of meaningful clinical results suggested by a panel of experts from the International Bladder Cancer Group (IBCG). In total, 58% of individuals with a CR had a DOR ≥12 months and 40% had a DOR ≥24 months. Adverse events were consistent with those reported with BCG alone. Serious adverse reactions occurred in 16% of individuals receiving Anktiva with BCG, with hematuria as the most common reaction, at 3.4%. A fatal adverse reaction of cardiac arrest occurred in 1.1% of individuals (1 individual) receiving Anktiva with BCG. Permanent discontinuation of Anktiva with BCG due to adverse reactions was observed in 7% of individuals. The primary adverse reaction leading to permanent discontinuation was musculoskeletal pain, affecting 2.3% of individuals. Dosage interruptions due to adverse reactions affected 34% of individuals receiving Anktiva with BCG.

References

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10. U.S. Food & Drug Administration. FDA approves first gene therapy for the treatment of high-risk, non-muscle-invasive bladder cancer. December 16, 2022. **https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-high-risk-non-muscle-invasive-bladder-cancer** Accessed February 11, 2025.

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History

Date	Comments
06/01/23	New policy, approved May 9, 2023. Added Adstiladrin (nadofaragene firadenovec-vncg) coverage criteria. HCPCS code J9999 added for Adstiladrin.
07/01/23	Coding update. Added new HCPCS code J9029.
07/01/24	Annual Review, approved June 11, 2024. Added Anktiva (nogapendekin alfa inbakicept-pmln) coverage criteria. Added HCPCS code J9030 for Anktiva. Policy title change from Adstiladrin (nadofaragene firadenovec-vncg) to Pharmacologic Treatment of Bladder Cancer.
09/01/24	Coding update. Removed HCPCS code J9030 as it has been added in error. Added HCPCS code C9399 to report Anktiva.
10/01/24	Coding update. Added new HCPCS code C9169 to report Anktiva. Removed unlisted code, C9399.
03/01/25	Annual Review, approved February 24, 2025. Added new HCPCS code J9028. Removed unlisted HCPCS code J9999. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.