MASSACHUSETTS

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Medical Policy

Gene Therapies for Bladder Cancer

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Policy Number: 159

BCBSA Reference Number: N/A
NCD/LCD: N/A

Related Policies

Prior Authorization request Form for Adstiladrin (nadofaragene firadenovec-vncg), #193

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Initial Approval Criteria

INITIAL APPROVAL: For up to 6 months

Nadofaragene firadenovec-vncg for the treatment of Bladder Cancer is considered **MEDICALLY NECESSARY** when **ALL** of the following criteria are met:

1. Patient has a diagnosis of non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (*with or without papillary tumors*); **AND**
2. Patient has high-risk disease that is unresponsive to Bacillus Calmette-Guerin (BCG) defined as:
    a. Persistent disease following adequate BCG therapy of at least five (5) of six (6) doses of an initial induction course of BCG followed by at least two (2) of three (3) doses of maintenance therapy or two (2) of six (6) doses of an additional induction course; **OR**
    b. Disease recurrence after an initial tumor-free state following adequate BCG therapy of at least five (5) of six (6) doses of an initial induction course of BCG followed by at least two (2) of three (3) doses of maintenance therapy or two (2) of six (6) doses of an additional induction course; **OR**
    c. Stage T1 disease following a single induction course of BCG; **AND**
3. Patient has undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components); **AND**
4. Patient does NOT have extra-vesical (i.e., urethra, ureter, or renal pelvis), muscle invasive (T2-T4), or metastatic urothelial carcinoma; **AND**
5. Individual is not currently receiving systemic therapy for bladder cancer; **AND**
6. Individual has not received any prior treatment with adenovirus-based therapies; **AND**

7. Patient does not have a hypersensitivity to interferon alfa; **AND**
8. Patient is not immunosuppressed or immunodeficient.

Renewal Criteria

CONTINUED APPROVAL – 12 months
Due to the increased risk of developing muscle-invasive or metastatic bladder cancer with delay in cystectomy, if patients with CIS do not have a complete response to treatment with Adstiladrin (Nadofaragene firadenovec-vncg) after 3 months or if CIS recurs, consider cystectomy.

Nadofaragene firadenovec-vncg approval can be renewed for continuation of care when **ALL the following criteria are met:**
1. Continues to meet initial approval criteria; **AND**
2. Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
3. Absence of unacceptable toxicity from the drug such as but not limited to disseminated adenovirus infection; **AND**
    a. For first renewal request, the patient had a complete response (CR) to initial therapy defined as a negative result for cystoscopy [with TURBT/biopsies as applicable] and urine cytology; **OR**
    b. For subsequent renewals the patient has not experienced a high-grade or CIS recurrence.

The use of Adstiladrin (nadofaragene firadenovec-vncg) for any other oncologic indication is considered **INVESTIGATIONAL** and therefore, not covered.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue℠	Prior authorization is **required**.
Medicare PPO Blue℠	Prior authorization is **required**.

Requesting Prior Authorization Using Authorization Manager
Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:
- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources
Refer to our Authorization Manager page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for Adstiladrin (nadofaragene firadenovec-vncg) (193) using Authorization Manager.

For out of network providers: Requests should still be faxed to 888-973-0726.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
J9029	Injection, nadofaragene firadenovec-vncg, per therapeutic dose

ICD-10 Procedure Codes

ICD-10 PCS Procedure Codes	Code Description
XW033F3	Introduction of Other New Technology Therapeutic Substance into Peripheral Vein, Percutaneous Approach, New Technology Group 3

Description

Bladder cancer is the sixth most common cancer in the United States, with an estimated 82,290 new cases and 16,710 deaths anticipated in 2023 (National Cancer Institute, 2023). Bladder cancer is more common in men compared with women, with men having a rate of 31.7 new cases per 100,000 individuals compared with 7.8 new cases per 100,00 individuals in women. Bladder cancer is also more common in white individuals compared with all other races or ethnicities. The risk of bladder cancer increases with age, with a median age at diagnosis of 73 years. Approximately three-quarters of new bladder cases are diagnosed as NMIBC (Balar, 2021). Patients with NMIBC who initially receive intravesical BCG immunotherapy generally have a strong initial response, with complete response rates at almost 75%; however, roughly 50% of patients will experience a recurrence within 5 years or will be BCG-unresponsive after two courses of therapy. Patients with BCG-unresponsive disease have a high risk of progression to muscle invasive disease.

Multiple risk factors for the development of bladder cancer have been identified (American Cancer Society [ACS], 2019a). Modifiable risk factors include smoking, which causes about half of all bladder cancers, workplace exposures to certain industrial chemicals, arsenic in drinking water, not drinking enough fluids, and exposure to certain medications or herbal supplements (e.g., Actos [pioglitazone], aristolochic acid). Nonmodifiable risk factors include being White, male, or at an older age; a history of bladder infections or chronic bladder irritation; a personal or family history of bladder or other urothelial cancers; a bladder birth defect; certain genetic mutations, such as those that cause retinoblastoma, Cowden disease, or Lynch syndrome; and prior exposure to cyclophosphamide or radiation to the pelvis.

The first sign of bladder cancer is most commonly gross or microscopic hematuria, although some patients may present with a urinary tract infection (ACS, 2019b; National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines in Oncology [NCCN Guidelines®], 2023). Patients can also experience changes in urination, such as more frequent urination, pain or burning during urination, having trouble urinating, or frequent nocturia. As bladder cancer progresses, patients can become unable to

urinate, experience unilateral lower back pain, appetite or weight loss, fatigue, swelling of feet, or bone pain.

BCG is the most effective therapy for high-risk non-muscle-invasive bladder cancer. Nadofaragene firadenovec (also known as rAd-IFNa/Syn3) is a replication-deficient recombinant adenovirus that delivers human interferon alfa-2b cDNA into the bladder epithelium, and a novel intravesical therapy for BCG-unresponsive non-muscle-invasive bladder cancer.

The 2023 NCCN Guidelines for the treatment of bladder cancer recommend that all patients undergo transurethral resection of bladder tumor (TURBT) followed by a single intravesical dose of off-label gemcitabine (Infugem) (preferred) or mitomycin (Mutamycin) within 24 hours of TURBT (NCCN Guidelines®, 2023). A summary of the NCCN recommendations for initial treatment following TURBT for patients with high-risk disease and treatment options for patients with persistent or recurrent disease is provided in the following table:

Disease Setting		Recommendations
Initial Therapy	**High-risk, BCG naïve**	• Cystectomy • BCG
	High-risk, BCG unresponsive or BCG intolerant	• Cystectomy (preferred) • Intravesical chemotherapy • Pembrolizumab (Keytruda) (select patients) • Nadofaragene firadenovec-vncg (Adstiladrin)
Persistent or Recurrent Disease	**BCG unresponsive**	• Cystectomy • Pembrolizumab (Keytruda) (select patients) • Nadofaragene firadenovec-vncg (Adstiladrin)
	Following BCG therapy	• Cystectomy • Pembrolizumab (Keytruda) (select patients) • Nadofaragene firadenovec-vncg (Adstiladrin) • Change intravesical agent†

Summary of Evidence

Nadofaragene firadenovec-vncg is a non-replicating adenoviral vector-based gene therapy designed to deliver a copy of a gene encoding a human interferon-alfa 2b to the bladder urothelium (Adstiladrin prescribing information, 2022). Intravesical instillation of Adstiladrin (nadofaragene firadenovec-vncg) results in cell transduction and transient local expression of the interferon-alfa 2b protein that is anticipated to have antitumor effects.

Nadofaragene firadenovec-vncg biodistribution and shedding were investigated in two clinical studies (Adstiladrin prescribing information, 2022). Only a single patient receiving a second dose in one study at dose level of 3×10^{11} viral particles/mL had measurable vector deoxyribonucleic acid (DNA) in blood; no other patients in either study had measurable vector DNA at 1 hour post-dosing in blood. In urine, measurable vector DNA was detected in both studies. Generally, a higher frequency of detection of urine samples positive for vector-derived DNA, and persistence of vector-derived DNA, correlated with increasing dose level.

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria
Boorjian, 2021 **Adstiladrin** 75 mL of 3×10^{11} viral particles/mL by intravesical instillation every 3 months* (N=151)	(N=51; N=103 for CIS cohort) **Study Design:** Phase III, ongoing, multicenter, single- arm, two-cohort, open-label trial **Primary Endpoint:** Complete response rate within 12	**Inclusion Criteria:** • Adults with BCG- unresponsive NMIBC† (CIS cohort: median age of 72 years, 89% male,93% White, 68% received • 2 or 3 previous BCG courses, 76% had CIS only, 26% had CIS + Ta or T1 tumor, 91% had ECOG

	months after the first dose of Adstiladrin in the CIS cohort **Secondary Endpoints:** • Duration of complete response • 12-month high- grade recurrence- free survival • 24-month overall survival	performance status of 0) • ECOG performance status of ≤ 2‡ • Life expectancy of ≥ 2 years **Exclusion Criteria:** • Evidence of upper urinary tract disease, urothelial carcinoma within the prostatic urethra, lymphovascular invasion, micropapillary disease, or hydronephrosis due to tumor • Current systemic therapy for bladder cancer or had received pelvic external beam radiotherapy within previous 5 years

Results	
Endpoint	**Adstiladrin** (N=103 for CIS cohort)
Complete Response Rate§ (95% CI)	53.4% (43.3 to 63.3)
Median Duration of Complete Response (95% CI)	9.7 months (9.2 to not estimable)
12-Month High-grade Recurrence-free Survival (95% CI)	24.3% (16.4 to 33.7)
24-month Overall Survival (95% CI)	91.2% (74.7 to 97.1)

- The median follow-up for the CIS cohort was 19.7 months.
- At month 12, 71% of patients in the CIS cohort developed recurrent high-grade NMIBC and 5% developed muscle invasive bladder cancer.
- Twenty-nine percent of patients in the CIS cohort underwent cystectomy by month 12, with a median time to cystectomy of 8.9 months; a post-hoc analysis found that patients who achieved a complete response had a significantly longer median time to cystectomy (11.3 months vs. 6.4 months; p = 0.043).

Safety

- Seventy percent of the safety population (N = 157) experienced drug-related adverse events. The most frequently reported drug-related adverse events (≥ 10%) were discharge around the catheter during instillation, fatigue, bladder spasm, micturition urgency, chills, dysuria, and pyrexia.
- Three patients discontinued treatment due adverse events (i.e., bladder spasms, discharge around the catheter during instillation, and urothelial hyperplasia).

Comments/Study Limitations: The CIS cohort included patients with CIS with or without concomitant high-grade Ta or T1 NMIBC and the high-grade Ta or T1 cohort included patients with high-grade Ta or T1 tumors without concomitant CIS; only data from the CIS cohort are shown. All visible tumors were required to be resected at the time of enrollment.

Conclusions: Adstiladrin demonstrated efficacy in patients with BCG-unresponsive NMIBC and was generally well-tolerated.

Policy History

Date	Action
9/2023	Policy clarified to include prior authorization requests using Authorization Manager.
6/2023	Policy created with literature and FDA prescriber information review. Effective 6/8/2023.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Boorjian SA, Alemozaffar M, Konety BR, et.al.(2021) Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol. 2021 Jan;22(1):107-117. doi: 10.1016/S1470-2045(20)30540-4. Epub 2020 Nov 27. PMID: 33253641; PMCID: PMC7988888.
2. Nadofaragene firadenovec-vncg [package insert]. Kupio, Finland: Ferring Pharmaceuticals; 2022
3. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP.(1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-655. PMID: 7165009.
4. Shore ND, Boorjian SA, Canter DJ, et.al.(2017) Intravesical rAd-IFNa/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin-Refractory or Relapsed Non-Muscle-Invasive Bladder Cancer: A Phase II Randomized Study. J Clin Oncol. 2017 Oct 20;35(30):3410-3416
5. Adstiladrin. Prescribing information. Ferring Pharmaceuticals; December 2022. Accessed June, 2023.
6. American Cancer Society. Bladder cancer risk factors. Revised January 30, 2019a. Accessed May 1, 2023. https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html
7. American Cancer Society. Bladder cancer signs and symptoms. Revised January 30, 2019b. Accessed May 1, 2023. https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/signs-and-symptoms.html
8. Oncology (NCCN Guidelines®) for Bladder Cancer V.2.2023. ©2023 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed May 1, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Network, Inc