BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 08/17/23**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 08/15/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

GENE THERAPY FOR NON-MUSCLE INVASIVE BLADDER CANCER

- **ADSTILADRIN® (nadofaragene firadenovec-vncg)**

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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- **ADSTILADRIN® (nadofaragene firadenovec-vncg)**

Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Adstiladrin (nadofaragene firadenovec-vncg) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:

   - High-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors with NMIBC defined as **ONE** of the following:

     a. Persistent disease following adequate BCG therapy (see Definitions section)
     b. Disease recurrence after an initial tumor-free state following adequate BCG therapy (see Definitions Section)
     c. T1 disease following a single induction course of BCG

   - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. There are **NO** contraindications, including hypersensitivity to interferon alfa or any component of the product.

5. Individual meets **AL**L of the following:

   - Has undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components)
   - Is ineligible or has elected not to undergo cystectomy

6. Individual does **NOT** meet **ANY** of the following:

   - Immunocompromised or immunodeficient
   - Extra-vesical (i.e., urethra, ureter, renal pelvis), muscle invasive (T2-T4), or metastatic urethral carcinoma
   - Concurrent use of systemic therapy for bladder cancer
   - Prior treatment with adenovirus-based therapies

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- **ADSTILADRIN® (nadofaragene firadenovec-vncg)**

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Adstiladrin (nadofaragene firadenovec-vncg) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist
  2. Individual's condition has responded while on therapy with response defined as **BOTH** of the following:
     - No evidence of high-grade carcinoma or carcinoma in situ (CIS)
     - No unacceptable disease drug toxicity
  3. Individual has been adherent with the medication
  4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use including disseminated adenovirus infection
  5. Individual does **NOT** meet **ANY** of the following:
     - Immunocompromised or immunodeficient
     - Extra-vesical (i.e., urethra, ureter, renal pelvis), muscle invasive (T2-T4), or metastatic urethral carcinoma
     - Concurrent use of systemic therapy for bladder cancer

  Renewal duration: 12 months

- If there is no complete response to treatment with Adstiladrin (Nadofaragene firadenovec-vncg) after 3 months or if CIS recurs, consider cystectomy due to the increased risk of developing muscle-invasive or metastatic bladder cancer with delay in cystectomy.

- Adstiladrin (nadofaragene firadenovec-vncg) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or

4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Adstiladrin (nadofaragene firadenovec-vncg) is indicated for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-Muscle Invasive Bladder Cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

Adstiladrin is a non-replicating adenoviral vector-based gene therapy designed to deliver a copy of a gene encoding a human interferon-alfa 2b (IFNα2b) to the bladder urothelium. Intravesical instillation of Adstiladrin results in cell transduction and transient local expression of the IFNα2b protein that is anticipated to have anti-tumor effects.

Approximately 70 percent of new urothelial bladder cancer are NMIBC which include Ta (papillary), T1 (submucosal invasive) and Tis (carcinoma in situ). Initial treatment is transurethral resection of urethral bladder tumor (TURBT) which should include biopsies of suspected CIS or areas of concern. For high-risk disease, intravesical therapy, primarily BCG is administered. There are limited second line treatment options for high-risk disease and cystectomy is preferred however often times individuals are not candidates or do not wish to proceed. Alternative intravesical therapy are also options, including chemotherapy such as sequential gemcitabine/docetaxel, mitomycin, etc., or gene therapy with Adstiladrin.

Definitions:

Adequate Bacillus Calmette-Guérin (BCG) therapy:

- 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
  - At least TWO of SIX doses of a second induction course

AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*		
Low Risk	Intermediate Risk	High Risk
▪ Papillary urothelial neoplasm of low malignant potential ▪ Low grade urothelial carcinoma - Ta and	▪ Low grade urothelial carcinoma - T1 or - >3 cm or - Multifocal or	▪ High grade urothelial carcinoma - CIS or - T1 or

- ≤3 cm and - Solitary	- Recurrence within 1 year ▪ High grade urothelial carcinoma - Ta and - ≤3 cm and - Solitary	- >3 cm or - Multifocal ▪ Very high-risk features (any): - BCG unresponsive - Variant histologies Lymphovascular invasion - Prostatic urethral invasion
*Within each of these risk strata an individual patient may have more or fewer concerning features that can influence care. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.		

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	08/15/24	Review with revisions: criteria
Pharmacy and Therapeutics Committee	08/17/23	Approved guideline
Clinical Pharmacist	06/22/23	Development

Coding:

HCPCS: J9029

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Resources:

Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Adstiladrin (nadofaragene firadenovec-vncg). Prescribing information. Ferring Pharmaceuticals; May 2024 at DailyMed http://dailymed.nlm.nih.gov. Accessed May 17, 2024.

2. Atlas SJ, Touchette DR, Beinfeld M, et al. Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-Unresponsive, Non-Muscle Invasive Bladder Cancer: Effectiveness and Value; Final Report. Institute for Clinical and Economic Review, December 17, 2020. https://icer.org/assessment/bladder-cancer-2020/#timeline. Accessed June 13, 2023.

3. Black, P, Kassouf W. Management of recurrent or persistent non-muscle invasive bladder cancer. In: UpToDate, Lerner SP, Shah S (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated April 13, 2023. Accessed May 17, 2024.

4. Boorjian SA, Alemozaffar M, Konety BR, et al. 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.

5. Kassouf W, Black P. Treatment of primary non-muscle invasive urethral bladder cancer. In: UpToDate, Lerner SP, Shah S (Eds). UpToDate, Waltham, MA.: Available at http://uptodate.com. Topic last updated June 14, 2022. Accessed May 17, 2024.

6. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Bladder Cancer. Version 4.2024. Updated 05/09/2024; https://www.nccn.org. Accessed May 17, 2024.

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html