Molina Clinical Policy
Adstiladrin (nadofaragene firadenovec-vncg): MEDICARE
Policy No. 438b

Last Approval: 12/11/2024
Next Review Due By: June 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of the Federal government or CMS for Medicare. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Bladder cancer of the bladder is the most common malignancy of the urinary system and the sixth most common cancer in the United States. Urothelial cell carcinoma is the most common type in the United States. The most common presenting symptom of bladder cancer is painless hematuria. Bladder tumors are typically confirmed via visualization during a cystoscopy and transurethral resection of a bladder tumor. Patients are risk stratified per the American Urological Association and Society of Urologic Oncology published standard guidance on the diagnosis of bladder cancer. After removal of visible cancer, treatment of non-muscle invasive bladder cancer (NMIBC) is often treated with bacillus Calmette-Guerin (BCG) (Chang 2021).

Gene therapy augments, replaces, or suppresses missing or mutated, dysfunctional genes with functional gene copies using a vector to carry the functional gene into the cell. The goal is to address the root cause of an inherited disease and provide a lasting therapeutic effect by enabling the affected cells or organs to produce normally functioning protein(s) or discontinue production of harmful protein(s), potentially restoring normal function in diseased cells or organs and slowing or reversing disease progression. Traditional gene therapy uses a vector to replace a dysfunctional gene, however gene therapies are increasingly used in diverse ways. The recent FDA-approved gene therapy is an antineoplastic agent used to modify biological responses by increasing interferon production.

Nadofaragene firadenovec-vncg (Adstiladrin), referred to in this policy as nadofaragene, 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 nadofaragene results in cell transduction and transient local expression of the IFNα2b protein that is anticipated to have anti-tumor effects. Nadofaragene is the first FDA-approved gene therapy used to increase expression of interferon production to treat high-risk BCG-NMIBC. This is a novel method of therapy.

COVERAGE POLICY

<u>All Gene Therapy requests require Molina Medical Director review.</u>

Nadofaragene firadenovec-vncg for the treatment of bladder cancer may be **considered medically necessary** when **ALL** the following clinical criteria are met:

1. Diagnosis of confirmed high-risk, BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary tumors
   Informational note: BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS remains a NCCN category 2B recommendation.

2. Member characteristics include **ALL** the following:
   a. Age 18 or older
   b. Eastern Cooperative Oncology Group (ECOG) status of 2 or less

c. No evidence of upper urinary tract disease
d. No evidence of urothelial carcinoma within the prostatic urethra
e. No evidence of lymphovascular invasion
f. No evidence of micropapillary disease
g. No hydronephrosis
h. No prior pelvic radiation therapy
i. No current signs of cystitis or urinary tract infection at treatment
j. No history of other malignancy within the past 5 years except treated skin cancer (basal or squamous cell) or upper tract urothelial cancer at least 24 months after nephroureterectomy

3. Member is not on immunosuppression (Category X)
4. Member does not have other comorbid factors with a life expectancy < 2 years)
5. Female members of childbearing age cannot be pregnant or lactating and must be willing to use maximal effective birth control (2 methods) or surgically sterile. Male members must be willing to use double barrier contraception or surgically sterile
6. Member is not on current systemic therapy for bladder cancer
7. Member has not had prior treatment with adenovirus-based drugs
8. Member can hold an instillation for 1 hour

CONTINUATION OF THERAPY

Continued treatment may be authorized provided there is not high-risk recurrence. See dosing considerations below.

LIMITATIONS AND EXCLUSIONS

The following are **considered contraindications** based on labelling:

1. Hypersensitivity to interferon alpha or any component of the formulation

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:

1. Any indications other than those listed above

DURATION OF APPROVAL: Up to six months with appropriate recurrence evaluation.

AGE RESTRICTIONS: 18 years of age and older.

DOSING CONSIDERATIONS:

1. Recommended dose: Single dose 75 ml of nadofaragene (3×10^{11} vector genomes [vg]) administered via intravesical route.
2. Repeat dosing may be given at 3, 6, and 9 months, up to a year provided the member does not have any high-grade recurrence. Cystectomy should be considered if complete response to nadofaragene does not occur after 3 months or if CIS recurs in those patients with BCG-unresponsive CIS.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The FDA approval of nadofaragene was based on Phase I and Phase II clinical studies and one multicenter open-label phase 3 randomized controlled trial (RCT) efficacy and safety study (n=198) for patients with BCG Unresponsive NMIBC unlikely to benefit from further intravesical BCG.

Phase 3 Trial. FDA approval of nadofaragene was primarily based on the results of an open label, repeat dose phase 3 randomized controlled trial (RCT) of patients aged 18 and older across thirty-three hospitals and clinics in the United States. Members were enrolled between September 2016 and May 2019.

- IFN a2b has effects that aid antitumor activity in NMIBC
- Adstiladrin is a non-replicating adenovirus vendor which harbors the IFN a2b gene which when combined with the excipient Syn3, intravesical administration results in transduction of the virus into the epithelial cells lining the bladder.

Primary Outcome Measure: The number of patients with a complete response rate over 12 months. This was deemed achieved when urine cytology was normal, atypical, degenerative, reactive, inflammatory, or nonspecific AND cystoscopy was normal or with findings that did not include evidence of low- or high-grade recurrence. Biopsy was not mandatory but if performed also did not include evidence of low-or high-grade recurrence.

Secondary Outcome Measures: All up to 60 months except as noted below:

- Durability of complete response
- Rate of event-free survival (High-grade recurrence free survival in patients with high-grade Ta or T1 disease (without CIS)
- Durability of event-free survival (Event free survival in patients with high-grade Ta or T1 papillary disease (without CIS)
- Incidence of cystectomy
- Overall survival
- Anti-adenoviral antibody levels and response rate correlation (only measured up to 12 months)
- Adverse events

Results. Between September of 2016 and May 2019, 198 patients were screened. Forty-one were excluded and 157 enrolled and received study drug. Six patients were provided study drug but did not meet the definition of BCG-unresponsive NMIBC and were excluded from analysis. Fifty-five (53.4%) of 103 patients with CIS (with or without a high-grade Ta/T1 tumor) had a complete response within 3 months. The response was maintained in 25 (45.5%) of 55 patients at 12 months. For those with only Ta/T1 disease the response rate was 72.9%. Treatment associated adverse events were common with 146 (93%) reporting at least one. Fourteen of the treatment associated adverse events were found to be serious with only three patients (2%) discontinuing due to adverse events. Urinary urgency was the most common grade 3-4 study drug related adverse event. This occurred in 2/157 or 1% of enrolled patients. For patients in the papillary disease cohort treatment associated adverse events were principally transient. Patients in this cohort experienced instillation site discharge 30%, bladder spasm, urinary tract infection, and micturition urgency all 18%. There were no treatment related deaths in the study.

Long-term follow-up data indicating durability of responses to nadofaragene are lacking presently. A long-term follow-up study in patients who received treatment is ongoing. This has been presented in abstract form. The patient results of this ongoing open label Phase 3 study enrolled 107 BCG-unresponsive, CIS±Ta/T1 patients. One hundred and three were analyzed and followed every three months with a 5-site biopsy at 12 months. Members received continued nadofaragene every 3 months up to 12 months and continued treatment every 3 months at the investigator's discretion. Data was cutoff in September of 2020, however 64/103 (62.1%) of the cohort remained on study with mean follow up of 23.5 months and 18/103 (17.5%) pts had received 24 months of treatment. Of the 55 CIS±Ta/T1 patients who achieved complete remission following treatment, 20 (36.4%) remained free of high-grade recurrence at 24 months. By 24 months 33/103 (32%) pts had undergone cystectomy. During this follow up two patients (1.9%)

discontinued treatment due to drug related adverse events.

Systematic Reviews/Meta-Analyses. No systematic reviews or meta-analyses pertaining to nadofaragene for the treatment of BCG unresponsive NMIBC were found during the literature search.

National and Specialty Organizations

The **American Urological Association (AUA)** (2020) clinical practice guideline titled *Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline* was updated in 2024. The recommendations favor surgical options for those resistant to BCG. For those unwilling or unfit for cystectomy, and in patients with persistent or recurrent high-grade NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle), a clinician may recommend clinical trial enrollment, an alternative intravesical therapy (i.e., nadofaragene [firadenovec-vncg]) or alternative intravesical chemotherapies (gemcitabine/docetaxel). A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy. (Conditional Recommendation; Evidence Strength: Grade C).

The **National Comprehensive Cancer Network (NCCN)** (2024) clinical practice guideline in *Oncology for Bladder Cancer (version 2.2023)* states:

> Nadofaragene firadenovec-vncg may be considered for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (category 2A) or for patients with BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS (category 2B). Cystectomy is preferred.

SUPPLEMENTAL INFORMATION

Adeno-associated viruses (AAV) are frequently utilized due to their unique biology and simple structure. These viruses are in the parvovirus family and are dependent on co-infection with other viruses, usually adenoviruses, to replicate. AAVs are poorly immunogenic compared with other viruses but can still trigger immune response. There are over one hundred different AAVs and 12 serotypes. Drug labeling information recommends avoidance to members who are on systemic immunosuppressants or chemotherapeutics.

CODING & BILLING INFORMATION

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J9029	Intravesical instillation, nadofaragene firadenovec-vncg, per therapeutic dose

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Added requirement of Molina Medical Director review.
06/12/2024	Annual review, no changes to coverage policy. Duration of approval and Summary of Evidence updated.
06/14/2023	New policy. IRO Peer Review in May 2023 by practicing, board-certified physicians with specialties in Urology and Oncology.

REFERENCES

1. 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. doi: 10.1016/S1470-2045(20)30540-4. Epub 2020 Nov 27. PMID: 33253641; PMCID: PMC7988888.
2. Chamie K, Chang SS, Kramolowsky E, et al. IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer. NEJM Evid. 2023 Jan;2(1):EVIDoa2200167. doi: 10.1056/EVIDoa2200167. Epub 2022 Nov 10. PMID: 38320011.
3. Chang SS. Urological Oncology: Bladder, penis and urethral cancer, and basic principles of oncology. J Urol. 2021 Nov;206(5):1326-1328. doi: 10.1097/JU.0000000000002156. Epub 2021 Aug 16. PMID: 34392695.
4. Holzbeierlein J, Bixler BR, Buckley DI, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/SUO guideline (2017; amended 2020, 2024). J Urol. Published online April 25, 2024. doi:10.1097/JU.0000000000003981
5. Nadofaragene Firadenovec and Oportuzumab Monatox for BCG-unresponsive, non-muscle invasive bladder cancer: effectiveness and value final report. Published Date Unknown. Cited May 7, 2023. Available from: https://icer.org/wp-content/uploads/2020/08/ICER_Bladder_Cancer_Final_Report_07292022.pdf.
6. National Comprehensive Cancer Network. Bladder cancer (version 4.2024). Published May 9, 2024. Available from: https://www.nccn.org.